Antithrombotic Therapy in Patients with Atrial Fibrillation: the Tasmanian Experience

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Abbreviations

Abbreviation	Explanation
AACP	American College of Chest Physicians
AC	Anticoagulant
ACS	Acute coronary syndromes
ACTIVE-W	Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events
ADP	Adenosine diphosphate
AF	Atrial Fibrillation
AHA/ACC/HRS	American Heart Association/American College of Cardiology/ Heart Rhythm Society
ALT	Alanine Aminotransferase
ANNEXA-A	Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity-Apixaban
ANNEXA-R	Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity-Rivaroxaban
AP	Antiplatelet
AR-DRG	Australian Refined Diagnosis Related Group
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AST	Aspartate Aminotransferase
ATRIUM	Outpatient Registry Upon Morbidity of Atrial Fibrillation
ATT	Antithrombotic therapy

Abbreviation	Explanation
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged
CCI	Charlson comorbidity index
CCS	Canadian Cardiovascular Society
CHF	Congestive Heart Failure
CIs	Contraindications
CI	Confidence interval
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CVA	Cerebrovascular accident
CYP450	Cytochrome P450
DDIs	Drug-drug interactions
DMR	Digital Medical Records
DOACs	Direct Oral Anticoagulants
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ENGAGE AF-TIMI 48	The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48
EORP-AF	EURObservational Research Programme Atrial Fibrillation
ESC	European Society for Cardiology
FDA	United States Food and Drugs Administration

Abbreviation	Explanation
GARFIELD	Global Anticoagulant Registry in the FIELD
GFR	Glomerular filtration rate
GIB	Gastrointestinal bleeding
GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation
H_2Bs	Histamine-2 receptor blockers
HF	Heart failure
HR	Hazard ratio
HTN	Hypertension
ICD-10	International Classification of Disease 10 coding system
ICERs	Incremental cost-effectiveness ratios
ICH	Intracranial haemorrhage
IDA	Idarucizumab
INR	International Normalised Ratio
IQR	Interquartile range
LGH	Launceston General Hospital
LMWH	Low molecular weight heparin
MI	Myocardial infarction
NICE	National Institute for Health and Clinical Excellence
NOAC s	Non-VKA Oral Anticoagulants
NSAIDs	Non-steroidal anti-inflammatory drugs
NT	No therapy
NVAF	Non-Valvular Atrial Fibrillation
NWRH	North West Regional Hospital

Abbreviation	Explanation
OACs	Oral Anticoagulants
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OR	Odds ratio
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
POC	Point-of-care
PPIs	Proton pump inhibitors
PVD	Peripheral Vascular Disease
PY	Person Years
QALY	Quality-adjusted life year
QoL	Quality of Life
RE-LY	Randomised Evaluation of Long-term anticoagulation therapy
RE-VERSE AD	REVERSAL Effects of Idarucizumab in Patients on Active Dabigatran
RHH	Royal Hobart Hospital
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	Risk ratio
SD	Standard deviation
SE	Systemic embolism
SPAF	Stroke Prevention in Atrial Fibrillation

Abbreviation	Explanation
SPORTIF	Stroke Prevention using an Oral Thrombin Inhibitor in atrial Fibrillation
TAF	Tasmanian Atrial Fibrillation Study
TE	Thromboembolism
TIA	Transient Ischaemic Attack
TTR	Time in therapeutic range
USA	United States of America
VKA	Vitamin K Antagonist
WTP	Willingness to pay

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder and is increasing in incidence and prevalence in ageing populations. It is estimated that 1.5-2% of the developed world suffers from AF. The risk of stroke and thromboembolism (TE) is increased 4-5 fold by non-valvular atrial fibrillation (NVAF) and nearly 15% of all strokes are caused by AF. Judicious use of antithrombotic therapy significantly reduces the risk of stroke for most patients who have AF. Conversely, underuse of antithrombotic therapy is associated with an increase in the rates of death and ischaemic events (stroke, transient ischaemic attack [TIA], or myocardial infarction [MI]). Despite the proven benefits of anticoagulant therapy among high-risk patients with AF, there have been frequent reports of discordance between guideline recommendations and anticoagulant prescribing patterns leading to problem of underutilisation in patients with AF in real-world practices.

During the time period of this study there were limited data available on the characteristics, clinical management and outcomes of patients with AF from an Australian perspective. The available literature suggested that there was underutilisation of anticoagulant therapy, although this data came from relatively small observational trials in selected patient groups. The Commonwealth Review of Anticoagulation Therapies in AF in Australia identified that stroke prevention in individuals with AF required improvement, and highlighted a range of issues to be addressed related to the assessment of patients for stroke and bleeding risk, appropriate choice of antithrombotic agent(s) in patients with multiple comorbidities, and the monitoring of patients. The review stressed the need for local data on which to base recommendations regarding the treatment of AF. Meanwhile, little was known about the clinical outcomes and safety of direct oral anticoagulants (DOACs) outside the trial setting. In 2011, dabigatran's sponsor launched a patient familiarisation program in which

over 28,000 Australians were enrolled. Thus, we established that there was a critical need for local data regarding the safety of antithrombotic medications, including the DOACs, in the treatment of AF. We designed this study, the Tasmanian AF (TAF) Study, as a starting point to providing comprehensive data describing the outcomes of stroke prevention strategies in Tasmanian patients with AF. The TAF study is an ongoing retrospective study that enrols patients from 3 different hospitals in Tasmania, Australia; the Royal Hobart Hospital (RHH), Launceston General Hospital (LGH) and North West Regional Hospital (NWRH). The rationale behind this project was to derive local data on usage pattern of antithrombotic therapy, clinical outcomes and their safety profile in Australian sub-population - initially prior to the Pharmaceutical Benefits Scheme (PBS) listing of DOACs, and then to use the established database to monitor the impact of the introduction of the DOACs into clinical practice.

Our main objectives in the work reported here were to retrospectively i) review the patient characteristics and antithrombotic treatment patterns among patients with AF in Tasmanian hospitals, ii) compare the anticoagulant utilisation to earlier data in the same population and identify predictors of anticoagulant prescribing among patients with NVAF, iii) evaluate the rates of, and factors associated with, hospital readmissions due to bleeding or TE complications among patients newly diagnosed with AF, and iv) compare the patient characteristics, antithrombotic prescribing patterns, and rates of bleeding or TE outcomes between older and younger patients diagnosed with AF.

To study the patient characteristics and antithrombotic prescribing patterns we reviewed and followed patients with AF admitted to Tasmania's 3 major hospitals between January 2011 and June 2012. In identifying the predictors of anticoagulant prescribing among

patients with NVAF and to compare the anticoagulant utilisation pattern to earlier data in the same population, we reviewed patients only with NVAF from the above population. To examine the rates of, and factors associated, with hospital readmission due to bleeding and TE, we recruited patients newly diagnosed with AF and admitted to the RHH between 1st January 2011 and 30th June 2012 and followed them for the first 3 months, and then at least 18 months, from the time of hospital discharge after their index admission. During short-term follow-up, patients were followed for 3 months from time of hospital discharge after their index admission with newly diagnosed AF or until the occurrence of a primary outcome or death, whichever came first. Similarly, for longer-term follow-up, patients were followed for at least 18 months from time of hospital discharge after their index admission with newly diagnosed AF, or until the occurrence of a primary outcome, death or December 31, 2013, whichever occurred first. Finally, to compare the patient characteristics, antithrombotic prescribing patterns, and rates of bleeding or TE outcomes between older and younger patients diagnosed with AF, we divided patients into two age groups - a younger group aged <75 and an older group aged 75 or above. Included patients were then followed from their index admission for at least 18 months from time of hospital discharge after their index admission or until the occurrence of a primary outcome, death or December 31, 2013, whichever occurred first. Our primary outcomes were readmissions due to: 1) major bleeding, including haemorrhagic stroke requiring hospitalisation, and 2) TE (ischaemic stroke and systemic embolism, MI and TIA).

Our patient population demonstrated high rates of comorbid conditions, especially cardiovascular disease. Nevertheless, their characteristics proved to be largely similar to some of the populations studied in international registries. Our study also compares well to the patient cohorts studied in clinical trials comparing DOACs to warfarin, in terms of mean age

and stroke risk. As seen in other real-world studies we also observed discordance between AF guideline recommendations and anticoagulant prescribing patterns despite the high risk of stroke observed. We also observed the relatively high rate of prescribing of combination anticoagulant/antiplatelet therapy in patients newly initiated on therapy and among those with existing AF from admission to discharge. In another study designed to compare the anticoagulant utilisation pattern to 15 year earlier data in the same population, and identify the predictors of anticoagulant prescribing among patients with NVAF, we observed that while there has been improvement over the past 15 years, suboptimal use of anticoagulant therapy among high risk patients with NVAF remains common. Younger age (odds ratio [OR] 0.99, 95% CI 0.97-1.0; P=0.04), $CHADS_2$=1, relative to 0 (OR 1.68, 95% CI 1.07-2.63; P=0.02), CHF (OR 1.56, 95% CI 1.12-2.15; P=0.008) and embolic disease history (OR 1.77, 95% CI 1.09-2.86; P=0.02) were significant predictors of anticoagulant prescribing. Despite guideline recommendations, we did not observe $CHADS_2 \geq 2$ as a significant predictor of anticoagulant prescribing in our population.

In our study to evaluate the rates of, and factors associated with, hospital readmissions due to bleeding or TE complications among patients newly diagnosed with AF, the rates per 100 person-years (PY) of bleeding and TE-related readmissions within 3 months were 4.8 (95% CI 2.2-7.5) and 8.1 (95% CI 4.8-11.4), respectively. The rates per 100 PY of bleeding and TE-related readmissions during a mean of 2.1 years' follow-up were 1.5 (95% CI 0.02-3.0) and 3.7 (95% CI 1.4-6.0), respectively. Patients with peripheral vascular disease (PVD) (OR 8.1, 95% CI 1.3-52.1) and renal impairment (OR 15.1, 95% CI 2.3-101.2) were more likely to be readmitted for bleeding, while those with a history of MI (OR 6.3, 95% CI 2.2-18.1) were more likely to be readmitted for TE during longer-term follow-up. We thus

observed higher rates of bleeding or TE-related readmissions in the initial 3 months following AF diagnosis and initiation of treatment.

Finally in our study to compare the patient characteristics, antithrombotic prescribing patterns, and rates of bleeding or TE outcomes between older and younger patients diagnosed with AF, we observed that among high-risk patients aged ≥75 years, only 51.8% received anticoagulant treatment (vs. 64.6% in the younger group; P=0.02). After a mean follow-up of 2.2 years, elderly patients were observed to be at higher risk of major bleeding (hazard ratio (HR) 3.2, 95% CI) 1.4-7.5, P=0.004) but the incidence of TE did not differ significantly (HR 1.5, 95% CI 0.9-2.7, P=0.15) between the groups. Elderly patients prescribed anticoagulant therapy were at significantly higher risk of major bleeding (HR 3.0, 95% CI 1.1-8.3, P=0.02) but at similar risk of TE (HR 0.9, 95% CI 0.4-1.8, P=0.69) compared to those on no anticoagulant therapy. In this study, anticoagulant therapy was underused among high-risk elderly patients with AF compared to their younger counterparts. Elderly patients had higher incidence of major bleeding but similar risk of TE compared to younger patients in this cohort.

Our study provides some important findings from the Australian perspective. Despite improvements in the use of anticoagulant therapy among high-risk patients with AF over a period of time, our findings highlight a gap between the evidence-based risk stratification and antithrombotic management pattern among patients with AF in Tasmania. In the absence of contemporary local guidelines, there appears to be a need to better support prescribers to assist in the identification and quantification of patient risk according to accepted international guidelines to optimise thromboprophylaxis and reduce the risk of thromboembolic and bleeding complications in this vulnerable patient group. Given the fact

that suboptimal oral anticoagulant use in patients with AF and poor compliance with guidelines still persist despite a transition to a new era of anticoagulation featuring DOACs, these findings remain pertinent. It is also acknowledged that monitoring of the patients newly initiated on treatment could play a significant role in minimising fatal bleeding and TE-related events in these patients. Our findings regarding the predictors of bleeding or TE outcomes suggest several risk factors that should be considered as 'red flags' when managing patients with AF. Patients with these conditions need special attention when managing concomitant AF. In fact, these patient groups are a potential target for intervention in future AF studies so as to minimise the incidence of bleeding or TE-related hospitalisations. Finally, underuse of anticoagulant therapy among high-risk elderly patients could have been influenced by the higher bleeding risk in this cohort compared to the younger group. Our finding that the elderly cohort were at higher risk of major bleeding due to anticoagulant therapy compared to the younger group requires further investigations so as to identify associated reasons for such outcome.

Chapter 1

Chapter 1 Literature Review

1.1 Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder and is increasing in incidence and prevalence in aging populations.(1) The electrical impulse that triggers a normal cardiac contraction originates at regular intervals in the sinoatrial node, usually at a frequency of 60-100 beats per minute. The generated impulse spreads through the atria and enters the atrioventricular node. The impulse then propagates over the His-Purkinje system and invades all parts of ventricles. After the ventricular activation, contraction of all of the ventricular muscle is normally synchronous and haemodynamically effective.(2) In AF however, there is uncoordinated atrial activation and consequently ineffective atrial contraction.(3-5) The electrocardiogram (ECG) taken during AF includes 1) irregular R-R intervals, 2) absence of distinct repeating P waves, and 3) irregular atrial activity.(6) The definition of AF based on duration of episodes is shown in Table 1.1.(3, 5, 7)

1.2 Epidemiology of AF

It is estimated that 1.5-2% of the developed world suffers from AF.(8, 9) AF is known to affect 5% of individuals older than 65 years and 10% of those aged older than 80 years.(9) The burden of stroke in terms of absolute numbers of people affected around the world is increasing, especially in younger age groups and in low-to-middle-income countries.(10)

Table 1.1 Definitions of AF

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 days of onset.
Persistent AF	• Continuous AF that is sustained >7 days.
Long-standing persistent AF	• Continuous AF >12 month in duration.
Permanent AF	• When the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.

NVAF	• Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve. • AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF: atrial fibrillation; NVAF: non-valvular AF

1.3 Risk of stroke in AF

AF typically coexists with hypertension (HTN), heart failure, coronary artery disease, and diabetes mellitus.(9) Importantly, it significantly and independently increases the risk of mortality and morbidity due to stroke, thromboembolism (TE) and congestive heart failure (CHF).(11) The risk of stroke and TE is increased 4-5 fold by non-valvular atrial fibrillation (NVAF) and nearly 15% of all strokes are caused by AF.(12) The risk increases further with a previous history of stroke or transient ischaemic attacks (TIA).(13) Thromboembolism in patients with NVAF is secondary to emboli arising from the atrial cavities, particularly the left atrial appendage.(14) In fact, several mechanisms consistent with the Virchow triad for thrombogenesis have been postulated for AF-related stroke: 1) stasis in the left atrium causing flow abnormalities; 2) structural heart and vascular disease (e.g., mitral stenosis); and 3) abnormal coagulation and fibrinolysis.(13)

Strokes related to AF are associated with higher mortality, greater disability, longer hospital stays, poorer functional outcome, and lower chance of being discharged home.(15) Stroke prevention is therefore a vital component of AF management. All contemporary guidelines recommend stroke prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke.(7, 16)

1.4 Stroke risk stratification schemes in AF and guideline recommendations

Risk factor based approaches are used for stroke risk stratification purposes. Among several risk stratification models, the $CHADS_2$ [CHF, HTN, age $\geq$75 years, diabetes and previous

stroke or TIA] (17) score has been the most commonly used due to its simplicity and endorsement in several widely promulgated practice guidelines.(18) The available guidelines during our study time period also suggested the use of $CHADS_2$ score as a preferred stroke risk assessment scheme.(4, 16) However, there has been debate on the advantages and disadvantages of the $CHADS_2$ score, particularly its non-inclusion of many common stroke risk factors (e.g., age 65-74 years, vascular disease, female sex).(19)

In order to improve risk stratification for stroke, overcoming the limitations of $CHADS_2$, the CHA_2DS_2-VASc [CHF, HTN, diabetes, vascular disease (prior myocardial infarction (MI), peripheral artery disease or aortic plaque), age 65-74 years, female gender, age ≥75 years and previous stroke or TIA or TE] (20) score was introduced. The CHA_2DS_2-VASc score includes more of the common stroke risk factors observed in everyday clinical practice. The CHA_2DS_2-VASc score has been validated in multiple cohorts.(21-25) A validation study has revealed that with a CHA_2DS_2-VASc score of 0 the risk was 'truly low' and no reduction in thromboembolic rate occurred with vitamin K antagonist (VKA) treatment, whereas the thromboembolic rate was reduced in VKA-treated patients with $CHADS_2$ scores of 0-1 and a CHA_2DS_2-VASc score of 1.(25) Recent guideline thus recommend CHA_2DS_2-VASc score as a preferred stroke risk stratification tool due to its advantage in identifying 'truly low-risk' (score=0) patients who do not need antithrombotic therapy.(6, 7) The $CHADS_2$ score is, however, less discriminatory for 'truly low risk' patients with AF in whom anticoagulation may be associated with a net disadvantage.(26) In summary, CHA_2DS_2-VASc is now established as being superior to the $CHADS_2$ score in identifying the 'truly low risk' subjects with AF, and as good as $CHADS_2$ score in predicting the 'high risk' subjects.(27) Table 1.2 shows the two different stroke risk stratification schemes.

Guidance currently varies on the preferred option for stroke prevention when the CHA_2DS_2-VASc score=1 (for males); some of the recent guidelines however recommend an anticoagulant over single or multiple antiplatelet therapy.(6, 7) Truly low-risk patients with AF - essentially a CHA_2DS_2-VASc score=0 (males) or 1 (females with no other predisposing risk factors) - do not require antithrombotic therapy, while other patients with the score $\geq$1 should have an oral anticoagulant (OAC) as the preferred option (well-controlled warfarin or one of the new OAC drugs).(28) Guideline recommendations for stroke prophylaxis based on stroke risk scores are summarised in Table 1.3.

Table 1.2 Scoring the risk of thromboembolic complications in AF (6)

Definition and scores for $CHADS_2$ and CHA_2DS_2-VASc		**Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores**	
			Adjusted Stroke Rate (% per y)
$CHADS_2$	**Score**	**$CHADS_2$**	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 years	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		**CHA_2DS_2-VASc**	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 years	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65-74 years	1	6	9.8
Sex category (i.e., female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

AF: atrial fibrillation; HF: heart failure; MI: myocardial infarction; PAD: peripheral artery disease; TE: thromboembolism; and TIA: transient ischaemic attack

Table 1.3 Guideline recommendations for stroke prophylaxis based on stroke risk scores

Guideline	Preferred scoring method	Values	Recommendation
ESC 2010 (4)	$CHADS_2$	0	• Either aspirin or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin
		1	• Either OAC or aspirin Preferred: OAC rather than aspirin
		≥2	• OAC, either VKA or DOACs
ACCP 2012 (16)	$CHADS_2$	0	• Either aspirin alone or combination of aspirin and clopidogrel. Preferred: no antithrombotic therapy than antiplatelet agents
		1	• OAC instead of no therapy or antiplatelet therapy
		≥2	• OAC (either VKA or DOACs) instead of no therapy or antiplatelet therapy
AHA/ACC/HRS 2014 (6)	CHA_2DS_2-VASc	0	• No antithrombotic therapy
		1	• No therapy, or treatment with OAC or aspirin may be considered
		≥2	• OAC, either VKA or DOACs
ESC 2012 (7)	CHA_2DS_2-VASc	0	• No antithrombotic therapy
		1	• Consider OAC for men, assess HAS-BLED score
		≥2	• Offer OAC, assess HAS-BLED score
NICE 2014 (29)	CHA_2DS_2-VASc	0	• No antithrombotic therapy
		1	• Consider OAC, discuss options with patients
		≥2	• Offer OAC, discuss options with patients
CCS 2014 (30)	$CHADS_2$ (age ≥65 and vascular diseases are considered)	0	• No therapy, but aspirin is suggested for patients aged <65 years and with vascular disease
		≥1	• Female sex and vascular disease are not considered as sufficient reasons for OAC use • OAC should be used, including in patients aged ≥65 years and without other risk factors

ACCP: American College of Chest Physicians; AHA/ACC/HRS: American Heart Association/American College of Cardiology/ Heart Rhythm Society; CCS: Canadian Cardiovascular Society; DOACs: direct oral anticoagulants; ESC: European Society of Cardiology; NICE; National Institute for Health and Clinical Excellence; OAC: oral anticoagulants; VKA: vitamin K antagonists

1.5 Bleeding risk stratification in AF

It is important to evaluate bleeding risk in patients with AF, especially in cases in which antithrombotic therapy is being prescribed.(31) The decision to prescribe thromboprophylaxis needs to balance the risk of stroke against the risk of bleeding. Intracranial haemorrhage (ICH) is the most feared complication of anticoagulation therapy and confers a high risk of

death and disability.(32) The HAS-BLED [HTN, abnormal renal function, abnormal liver function, bleeding pre-disposition, age >65 years, the use of drugs predisposing patients to bleeding (non-steroidal anti-inflammatory drugs (NSAIDs)), alcohol use (>8 drinks per week), previous stroke and labile INRs] is a recently proposed bleeding risk score - see Table 1.4.(33)

Table 1.4 Clinical Characteristics Composing the HAS-BLED Bleeding Risk Score

HAS-BLED	Score
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs (e.g., TTR <60%, applies only if the patient is taking warfarin)	1
Elderly (age >65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum	**9 points**

INR: international normalised ratio; TTR: time in therapeutic range

The HAS-BLED score helps clinicians to make an informed assessment of bleeding risk. It has been validated in several independent cohorts (33-37) and correlates well with ICH risk. A formal bleeding risk assessment is recommended for all patients with AF and, in patients with a HAS-BLED score ≥3, caution and regular review are recommended.(7) As a general rule, OACs should be considered for all patients with AF, except those at very low risk for stroke (CHA_2DS_2-VASc score of 0) and those at extremely high risk for bleeding, so as to avoid the risk of unwanted bleeding.(38)

1.6 Antithrombotic therapy in AF

Stroke prevention is imperative to the management of AF. Without antithrombotic treatment, the annual risk of stroke in patient with NVAF increases from 5% in patients aged less than 65 years to 8% in patients 75 years of age or older.(39) Contemporary guidelines recommend prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke.(7, 16) A flowchart on how to choose antithrombotic therapy in patients with AF based on a guideline recommendation is shown in Figure 1.1.(7) A meta-analysis by Hart (40) revealed that judicious use of antithrombotic therapy reduces stroke for most patients who have AF. Options include the older antithrombotic drugs like warfarin, aspirin, and clopidogrel as well as the newer direct thrombin inhibitors and factor Xa inhibitors. Ideal anticoagulants should be efficacious, safe, and cost effective. The choice between these drugs for an individual patient depends on the existing clinical scenario and the patient's long-term risk of stroke. Thromboembolic risk factors due to AF and risk factors for bleeding due to oral antithrombotic therapy are largely the same, and bleeding risk very rarely outweighs the benefits of thrombosis prevention; hence, antithrombotic therapy is beneficial in almost all patients with AF.(26, 41, 42)

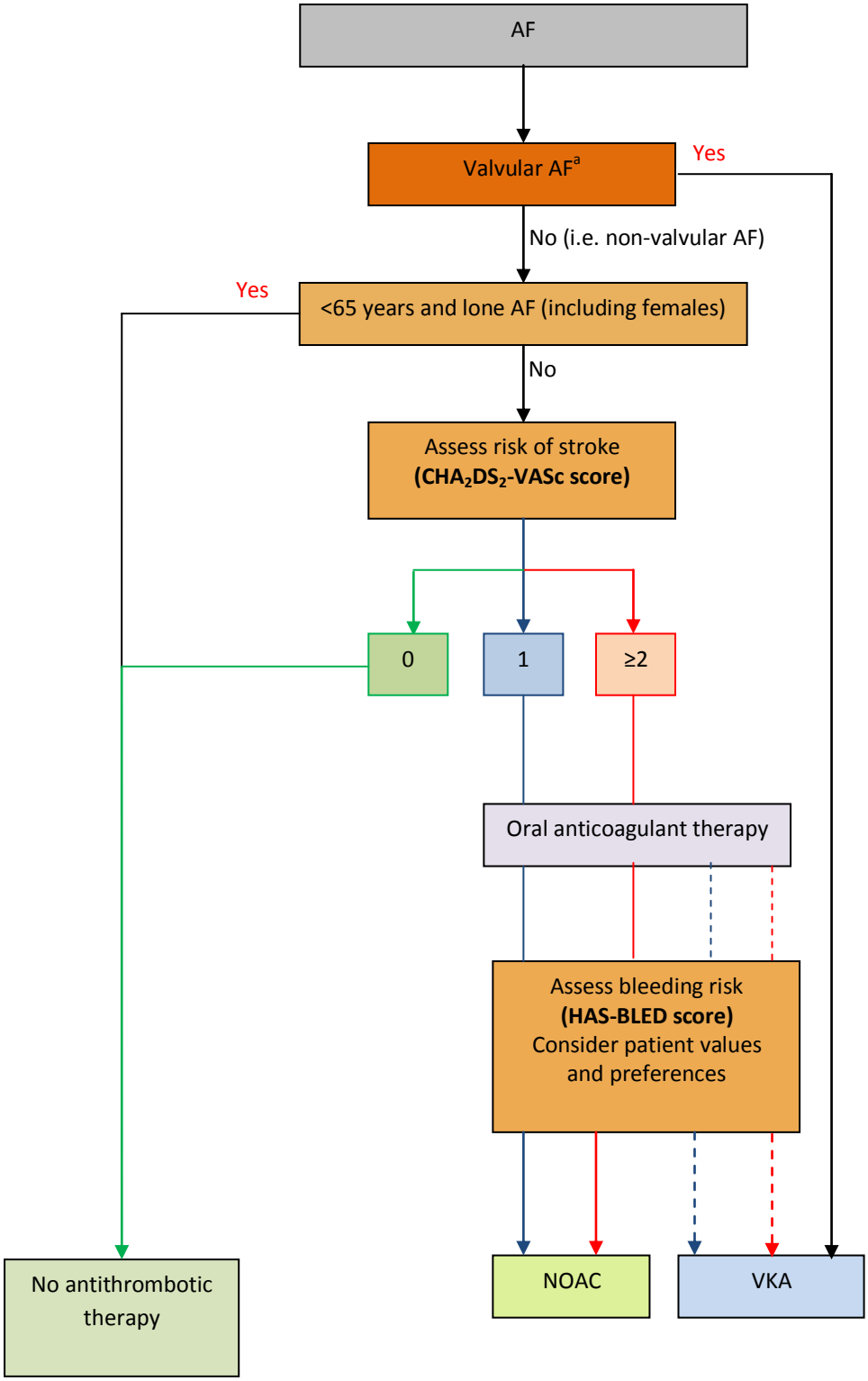


Figure 1.1: Choice of anticoagulant in AF

AF: atrial fibrillation; NOAC: non-VKA-oral anticoagulant; OAC: oral anticoagulant; VKA: vitamin K antagonist.

[a] Includes rheumatic valvular disease and prosthetic valves

Line: solid = best option; dashed = alternative option.

1.6.1 VKAs - Warfarin

Warfarin is known to exert its anticoagulant effect by inhibiting gamma-glutamyl carboxylation of vitamin K-dependent clotting factors II, VII, IX and X. The blockade results in incomplete coagulation factor molecules that are biologically inactive. Warfarin mainly prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone form as shown in Figure 1.2.(2)

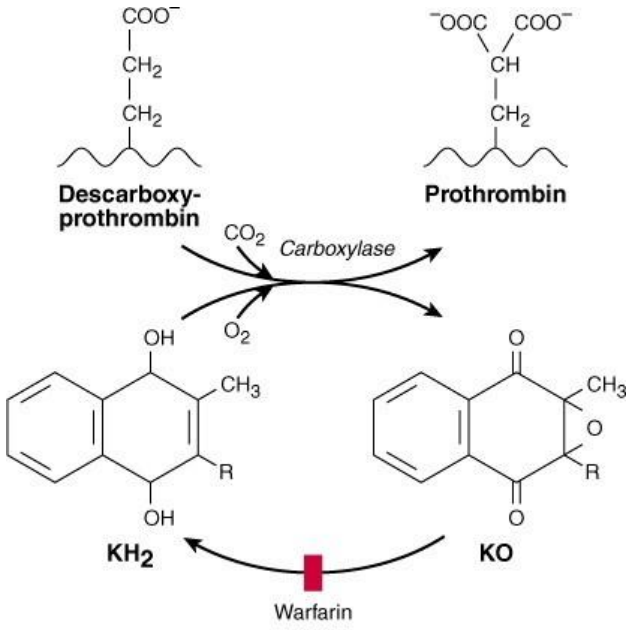


Figure 1.2: Mechanism of action of warfarin
KH_2: reduced vitamin K; KO: oxidised vitamin K

Despite the convincing evidence for the use of warfarin in AF, it is frequently reported as being underutilised.(43) Underuse of antithrombotic therapy is associated with an increase in the rate of death and ischaemic events, and increased overall health care costs.(44, 45) Improving the utilisation and adherence to OAC has been shown important to attaining the clinical and economic benefits of therapy.(45) Underuse of warfarin is often associated with its inherent pharmacological limitations, as listed below and requiring close monitoring:

1. Narrow therapeutic index,
2. Slow onset and offset of action,
3. Unpredictable pharmacodynamic and pharmacokinetic profiles, and
4. Multiple drug and food interactions.

Issues appear to exist with the quality of anticoagulation management with warfarin in long term use, because of fluctuations of INR values, due to multiple factors like genetic factors, poor compliance with medication, drug-drug interactions, and changes in diet.(46) For safe and effective stroke risk reduction with warfarin, the INR needs to be maintained in the range of 2.0-3.0 for at least 60% of the time.(47) Time in therapeutic range (TTR) is highly correlated with clinical outcomes; a poor TTR (<60%) is strongly associated with higher rates of mortality and major bleeding compared with moderate (60-75%) and good control (>75%).(48) A review has found that in patients with AF, a 7% improvement in TTR is associated with one less haemorrhagic event per 100 patient-years and a 12% improvement is associated with one less TE event per 100 patient-years.(49) A recent study conducted across western Europe revealed that overall anticoagulation management according to TTR was relatively homogenous and well-controlled in patients with AF, ranging from 70.3% in Spain to 81.4% in Germany.(50) However, the story may be different in developing countries. Data on the quality of anticoagulation achieved in developing countries was provided by the RE-LY trial (51), where the mean TTR was 56.9% for developing countries and 65.4% for developed countries. The mean TTR in 70.6% of developing countries represented in this trial (as classified by the World Bank (52)) demonstrated poor TTRs (<60%) or labile INRs, in contrast to the developed countries, where 81.5% of the participating countries obtained moderate TTRs (60-75%). Table 1.5 shows the TTRs of developed and developing countries in the same trial.

There are limited data available regarding INR control in Australia. The Commonwealth Review of Anticoagulation Therapies in AF in Australia identified the need to establish current warfarin control and determine the potential place of the new oral anticoagulants.(53) A retrospective study (54) conducted among 1137 patients to determine the quality INR control in southern Tasmania revealed that this group had a mean TTR of 69.1% and a mean testing interval of 22.9 days. The proportion of patients with a mean TTR <60% was 22.3% and 52.5% had a TTR >70%. This revealed better real world INR control in Tasmania compared to clinical trial results. Another retrospective study conducted to investigate the influence of pharmacist-led medication reviews on INR control in elderly patients in Tasmania observed the overall TTR of 64% and this was comparable to that achieved in recent randomised trials involving warfarin.(55) A recently conducted study among 3692 patients to determine warfarin control by a pathology practice in Queensland, Australia and identify factors influencing TTR observed a mean TTR of over 81% with 97% of patients above a TTR of 60%. TTR was not significantly influenced by age, gender or socioeconomic factors in this study.(56) These data demonstrate that dedicated warfarin programs can produce high quality care ensuring the full benefit of warfarin for Australian patients.(56)

Table 1.5 Quality of INR control in developed and developing countries in the RE-LY trial (51)

Time in therapeutic range (TTR)	Developed countries (n=27/44)	Developing countries (n=17/44)
<60% (poor)	4 (14.8%)	12 (70.6%)
60-75% (moderate)	22 (81.5%)	5 (29.4%)
>75% (good)	1 (3.7%)	0

INR: international normalised ratio

While it is acknowledged that comparison of TTR results has limitations associated with large variations in site performance and that this may be even more significant in developing countries due to the lack of standard disease management guidelines these data nevertheless illustrate the disparity in INR control between the developed and developing world, especially in the absence of more comprehensive indicators of anticoagulation quality (e.g. risk-adjusted TTR).(57) These results are significant as modelling has suggested that a minimum TTR threshold of 58% is necessary for a positive risk-benefit balance with warfarin use in AF (58); below this threshold, warfarin may result in poorer outcomes than antiplatelet therapy. This association between TTR and clinical outcomes was also apparent in the RE-LY study - rates of stroke and TE, as well as major bleeding, were greater among patients receiving warfarin with a TTR below 50%. Compared to dabigatran, warfarin was more cost-effective only when patients' TTR was greater than 72%.(51)

To overcome the limitations of warfarin, a number of direct oral anticoagulants (DOACs) are under development or have been marketed. Switching from warfarin therapy to DOACs is however advocated only if INR control has been poor or if frequent monitoring is

problematic.(59) Hence, the choice of agent should be dictated by a risk-benefit analysis based on an individual patient's characteristics.

1.6.2 DOACs

The DOACs for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban).(60) DOACs selectively block the formation of factor IIa and Xa, respectively, as shown in Figure 1.3.(2) DOACs are recommended when VKAs cannot be used because of difficulty in maintaining a therapeutic INR, adverse drug reactions, and inability to attend INR monitoring.(61) Though there is lack of head-head trials comparing the use of particular DOACs, specific recommendations for dabigatran etexilate and rivaroxaban are provided in the European guideline of 2012.(7)

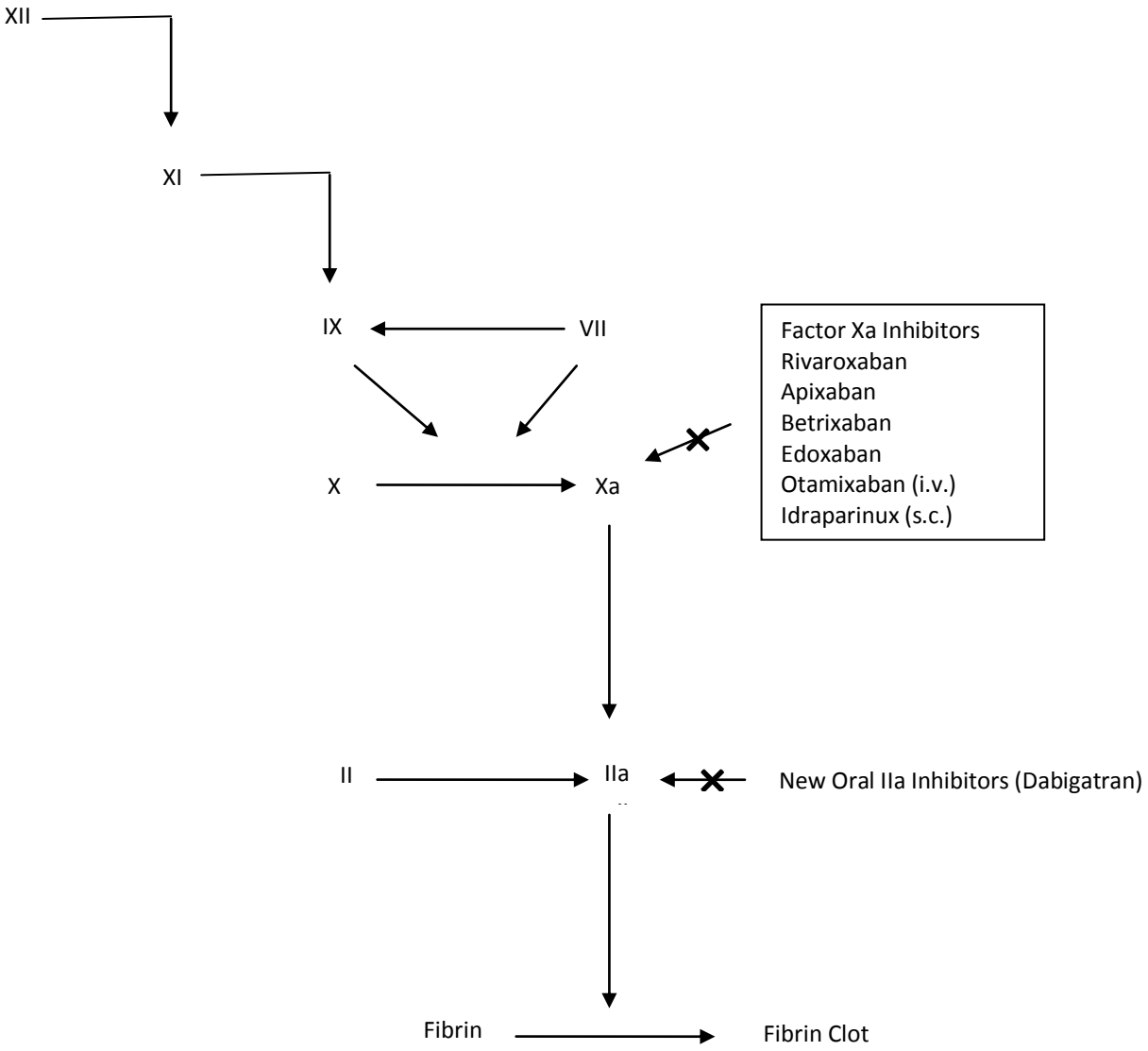


Figure 1.3: Mechanism of action of DOACs

1.6.2.1 Oral direct thrombin inhibitors

Dabigatran

Dabigatran etexilate is a prodrug of dabigatran. Dabigatran is a potent, highly specific, competitive, oral thrombin inhibitor that acts specifically both on bound and free thrombin.(62) The prodrug form of dabigatran etexilate is converted by serum esterases to the active drug dabigatran, thus making the prodrug form independent of CYP450 for the conversion, which ultimately makes drug-drug and drug-diet interactions less likely though some of them have been reported.(63, 64) Bioavailability of orally administered dabigatran is estimated to be about 6%, requiring relatively high doses for maintaining therapeutic plasma concentrations.(63) Use of dabigatran requires a rational dose individualisation and monitoring guidance particularly among patients at high risk of bleeding such as the elderly, overweight patients, and those with renal impairment (avoided in those with severe renal impairment: GFR <30ml/min) and/or on drugs with potential interactions.(65) The results of the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) (66) trial showed that dabigatran administered at a dose of 150mg given twice daily, as compared with warfarin, was associated with lower rates of stroke and systemic embolism (SE) but similar rates of major haemorrhage. On the other hand, the dosage regimen of 110mg given twice daily was shown to be non-inferior to warfarin with less incidence of bleeding.

1.6.2.2 Oral factor XA inhibitors

Rivaroxaban

Rivaroxaban is an oral factor Xa inhibitor, which is competitive and reversible in its mechanism and has a rapid onset of action and dose dependent pharmacokinetics and pharmacodynamics.(67-69) It attains peak plasma concentration in about 3 hours and has a bioavailability of 60-80%; it has terminal half-life of 5-9 hours in young individuals and approximately 11-13 hours in people older than 75 years.(69, 70) The phase III study

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K antagonists for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) (71) revealed that rivaroxaban was similar to warfarin for the primary efficacy endpoint of prevention of stroke and SE.

Apixaban

Apixaban is also a reversible, direct, and highly selective inhibitor of factor Xa. Apixaban and its metabolites are excreted by multiple elimination pathways, including renal excretion and metabolism. This suggests that patients with hepatic or renal impairment may be treated with apixaban and that the likelihood of significant drug-drug interactions may be low.(72)

The AVERROES (Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonists Treatment) (73) study was designed to determine the efficacy and safety of apixaban as compared to aspirin for the treatment of patients with AF for whom VKA therapy was considered unsuitable. The trial was stopped early due to significant reduction in the primary endpoint stroke or SE with apixaban (1.6% per year) compared to aspirin (3.7% per year). There was no significant difference in rates of major bleeding or ICH between apixaban (1.4% per year) and aspirin (1.2% per year). Another trial, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (74) comparing apixaban to warfarin found apixaban to be superior to warfarin at a dose of 5mg twice daily, significantly reducing the risk of stroke or SE by 21% and major bleeding by 31%.

Edoxaban

Edoxaban is an oral, direct and reversible factor Xa inhibitor.(75) The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation- Thrombolysis In

Myocardial Infarction 48 (ENGAGE AF-TIMI 48) (76) trial compared once daily low (30mg) and high dose (60mg) edoxaban to warfarin. High dose edoxaban was found to be non-inferior with respect to prevention of stroke or SE, with the same rate of ischaemic stroke as warfarin.

There are considerable differences in pharmacodynamic and pharmacokinetic properties between the individual DOACs.(77) Differences in the pharmacological properties of DOACs are shown in Table 1.6.(78) Comparison of the characteristics of the patients enrolled in different trials of DOACs is shown in Table 1.7.

Table 1.6 Pharmacological properties of DOACs

Characteristics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Direct target	Factor IIa (thrombin)	Factor Xa	Factor Xa	Factor Xa
Need for monitoring	No	No	No	No
Pro-drug	Yes	No	No	No
Bioavailability	≈6%	>80%	≈50%	≈50%
Time to reach peak plasma concentration (hours)	2-3	2-3	2-3	1-2
Half-life (hours)	14-17	5-13	8-15	6-11
Metabolism	P-gp	P-gp CYP3A4/3A5 CYP2J2	P-gp CYP3A4/3A5	P-gp CYP3A4
Renal elimination	>80%	≈50%	≈50%	≈50%

P-gp: P-glycoprotein

Table 1.7 Patient characteristics comparison between warfarin vs. DOACs clinical trials

Patient characteristics	RELY-AF (66) (n=18,113)	ROCKET AF (71) (n=14,264)	ARISTOTLE (74) (n=18,201)	ENGAGE-TIMI (76) (n=21,105)
Age in years	72	73	70	72
Males (%)	64	60	65	62
Comorbidities (%)				
CHF	32	62	35	58
HTN	79	90	87	94
Diabetes	23	40	25	36
Prior stroke/TIA	20	55	20	28
Prior MI	17	17	14	-
History of bleeding	-	-	-	-
AF type	NVAF	NVAF	NVAF	NVAF
New-onset AF	-	1.4%	-	-
Mean $CHADS_2$	2.1	3.5	3.5	2.8
Mean CHA_2DS_2-VASc	-	-	-	-

AF: atrial fibrillation; CHF: congestive heart failure; HTN: hypertension; MI: myocardial infarction; TIA: transient ischaemic attack

1.6.3 Antiplatelet therapy

1.6.3.1 Aspirin

Aspirin inhibits the synthesis of thromboxane A_2 by irreversible acetylation of the enzyme cyclooxygenase.(2) A meta-analysis by Hart (40) revealed that warfarin was more efficacious than antiplatelet therapy; adjusted-dose warfarin and antiplatelet agents reduced stroke by approximately 60% and 20%, respectively, in patients with AF. Antiplatelet therapy has limited utility for stroke prevention as the risk of bleeding is not different between aspirin and warfarin.(34, 41, 79) The efficacy of warfarin as prophylaxis against stroke and its benefits over antiplatelet therapies are well established.(80) Aspirin is only recommended for stroke prevention where patients refuse anticoagulation, and preferably given in combination with clopidogrel.(7)

1.6.3.2 Clopidogrel

Clopidogrel is a thienopyridine derivative that reduces platelet aggregation by inhibiting the adenosine diphosphate (ADP) pathway of platelet. It irreversibly blocks the ADP receptor on

platelet.(2) There is no evidence to support the use of clopidogrel monotherapy over aspirin or OAC in AF.(81)

1.6.3.3 Combination antiplatelet therapy

Studies have found that aspirin-clopidogrel combination therapy has additional efficacy as compared to aspirin monotherapy; however, the combination increases the risk for major bleeding.(82) The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) was a trial involving comparison of combination antiplatelet therapy (clopidogrel and aspirin) with warfarin. It was stopped early due to the clear evidence of superiority of OAC therapy, with the annual stroke risk on warfarin of 3.93% compared with annual stroke risk on clopidogrel plus aspirin of 5.6%.(81)

1.6.4 Anticoagulation plus antiplatelet therapy

The combination of fixed dose warfarin (INR 1.3) plus aspirin was found to be significantly inferior to full dose anticoagulation (INR 2-3) in Stroke Prevention in Atrial Fibrillation (SPAF) III trial.(83) Trials testing the combination of anticoagulation plus antiplatelet therapy have shown mixed results and there is absence of clear evidence for the benefit of combination therapy with full anticoagulation.(84)

Some of the studies have shown increases in the risk of haemorrhage with combination therapy of anticoagulation and antiplatelet agents.(85-87) Guidelines clearly mention that the usefulness of combination OAC and antiplatelet therapy particularly applies in patients with AF and acute coronary syndromes (ACS) or to those having percutaneous coronary intervention or stenting for up to 12 months after the procedure. However, for patients with AF and stable coronary artery disease only OAC is recommended rather than

combination of OAC and aspirin as combination therapy is associated with a significantly higher risk of bleeding.(16)

1.6.5 DOACs versus Warfarin

Dabigatran, rivaroxaban, apixaban and edoxaban have been compared to warfarin in patients with AF in four pivotal clinical trials.(66, 71, 74, 76) The data from these trials indicated that, generally, the DOACs are at least noninferior to warfarin in regards to the primary outcomes of stroke/SE and major bleeding, and are superior to warfarin with respect to the rate of intracranial bleeding and haemorrhagic stroke. The summary of phase III randomised clinical trials for DOACs is shown in Table 1.8. Most of these clinical trials involving DOACs have been conducted in developed countries, and their rapid uptake to date suggests that they will most likely displace warfarin in these countries in the near future.(88) However, developing countries may have more difficulties in adopting these drugs into practice. Issues related to the safety, efficacy and cost-effectiveness of DOACs could be the major hurdle for their approval in the developing world. Until further safety and efficacy data emerge, warfarin and aspirin are likely to continue as first line antithrombotic agents.

In a meta-analysis of 50,578 patients from 3 randomised trials that compared DOACs with warfarin in AF, it was found that DOACs decreased stroke or SE, haemorrhagic stroke and mortality, with a similar risk of major bleeding compared to warfarin.(89) DOACs were associated with lower rates of haemorrhagic stroke (0.3% vs. 0.8%, odds ratio (OR) 0.79, 95% CI 0.71-0.88, P<0.001) and intracranial bleeding (0.6% vs. 1.3%, P<0.001), and a higher rate of gastrointestinal bleeding (GIB) (2.3% vs. 1.3%, P=0.036). A systematic review (90) that compared the effectiveness of warfarin and DOACs for the management of AF and venous TE considered DOACs as a viable option for patients receiving long-term

anticoagulation. DOACs decreased all-cause mortality (risk ratio [RR], 0.88 [95% CI, 0.82 to 0.96]) and the adverse effects of DOACs compared with warfarin were fatal bleeding (RR, 0.60 [CI, 0.46 to 0.77]), major bleeding (RR, 0.80 [CI, 0.63 to 1.01]), GI bleeding (RR, 1.30 [CI, 0.97 to 1.73]), and discontinuation due to adverse events (RR, 1.23 [CI, 1.05 to 1.44]). The review, through its subgroup analysis, also suggested that the bleeding risk for DOACs may be increased in persons older than 75 years or those who had been receiving warfarin with good control. Similarly, a Chinese study (91) found that, after 1.9 years of follow-up, there was suboptimal or lower quality stroke prevention among 1034 patients with AF, with no difference between antiplatelet- and OAC-treated patients. Modelling analyses concluded that the use of apixaban or dabigatran could provide better stroke prevention compared to antiplatelet or warfarin use, with a positive net clinical benefit. A hospital-based Malaysian retrospective study (92), conducted among 510 patients between 2010 and 2013 to investigate the safety and efficacy of dabigatran in AF, found lower rates of ischaemic stroke, side effects and bleeding with dabigatran than in the RE-LY trial, and a high patient preference to switch from warfarin. These results provide reassurance that DOACs can be safer than warfarin, if prescribed appropriately.

A population-based descriptive analysis study (88) that looked into the prescribing patterns of DOACs following regulatory approval for AF in Ontario, Canada, between October 2010 and September 2012 found rapid growth in the uptake of DOACs, particularly dabigatran. The monthly prescriptions of DOACs increased more than 20-fold, from 16 to 336 prescriptions per 1000 000 population. Most of the dabigatran prescriptions were for the lower dosage (110 mg/d) in the older patient groups (58.8% of prescriptions in the 65-84 age group and 93.6% in the oldest group). This growth in the uptake of DOACs in very old

patients (i.e. those at the highest risk of bleeding) cautioned the need to evaluate outcomes in clinical practice to better guide the use of these drugs.

Despite the proven benefits of DOACs, there still remains significant uncertainty about the safety, effectiveness and cost-effectiveness of DOACs in widespread clinical use.(53) There have been reports of deaths related to dabigatran internationally.(93, 94) There is a need for ongoing clinical trials and real-world based observational studies to gather more information about DOACs. Few real-world based observational studies have been conducted in relation to comparing the safety and efficacy profile of warfarin vs. DOACs.(95-99) Several registries have also been established so as to generate important data regarding AF management practices in the real-world. Comparison of patient characteristics among some of these registries has been shown in Table 1.9. Summary of data regarding the outcomes of treatment relating to warfarin vs. DOACs in some of the observational real-world studies and registries have been shown in Table 1.10. A recent review of longitudinal observational studies comparing dabigatran with warfarin, summarised that, in real-world clinical practice, dabigatran was comparable with warfarin in preventing ischaemic stroke among patients with NVAF. However, dabigatran was found to have lower risk of intracranial bleeding relative to warfarin, but, particularly among elderly, a greater risk for GIB.(100)

Table 1.8 Clinical trials comparing Safety and efficacy outcomes of DOACs with warfarin in patients with NVAF (101, 102)

TRIAL	RE-LY (66) DABIGATRAN		ARISTOTLE (74) APIXABAN	ROCKET-AF (71) RIVAROXABAN	ENGAGE AF –TIMI 48 (76) EDOXABAN	
Number of patients	18,113		18,201	14,000	21,105	
Design	Open-labelled, non-inferior		Double-blind, double dummy, non-inferiority	Double-blind, double dummy, non-inferiority	Double-blind, double dummy	
Drug and dosages	Dabigatran 110mg twice daily versus warfarin	Dabigatran 150mg twice daily versus warfarin	Apixaban 5mg twice daily versus warfarin	Rivaroxaban 20mg once daily versus warfarin	Higher-dose edoxaban versus warfarin	Lower-dose edoxaban versus warfarin
Primary end point (% per year) stroke or SE	1.53% vs 1.69% p=0.34	1.11% vs 1.69% p<0.001	1.27% vs 1.60% p=0.01	2.12% vs 2.42% p=0.117	1.57% vs 1.80% p=0.08	2.04% vs 1.80% p=0.10
Ischaemic stroke (or unspecified)	1.34% vs 1.20% p=0.35	0.92% vs 1.20 p=0.03	0.97% vs 1.05% p=0.42	1.34% vs 1.42% p=0.581	1.25% vs 1.25% p=0.97	1.77% vs 1.25% p<0.001
Haemorrhagic stroke	0.12% vs 0.38% p<0.001	0.10% vs 0.38% p<0.001	0.24% vs 0.47% p<0.001	0.26% vs 0.44% p=0.024	0.26% vs 0.47% p<0.001	0.16% vs 0.47% p<0.001
Intracranial haemorrhage	0.23% vs 0.74% p<0.001	0.30% vs 0.74% p<0.001	0.33% vs 0.80% p<0.001	0.49% vs 0.74% p= 0.019	0.39% vs 0.85% p<0.001	0.26% vs 0.85% p<0.001
Major bleeding	2.71% vs 3.36% p=0.003	3.11% vs 0.74% p<0.001	2.13% vs 3.09% p<0.001	3.6% vs 3.45% p=0.576	2.75% vs 3.43% p<0.001	1.61% vs 3.43% p<0.001
Gastrointestinal bleeding	1.12% vs 1.02% p=0.43	1.51% vs 1.02% p<0.001	0.76% vs 0.86% p=0.37	3.15% vs 2.16% p<0.001	1.51% vs 1.23% p=0.03	0.82% vs 1.23% p<0.001
All-cause death	3.75% vs 4.13% p=0.43	3.64% vs 4.13% p=0.051	3.52% vs 3.94% p=0.046	1.87% vs 2.21% p=0.073	3.99% vs 4.35% p=0.08	3.80% vs 4.35% p=0.006
Vascular death	2.43% vs 2.69% p=0.21	2.28% vs 2.69% p=0.04	1.80% vs 2.02% p>0.05	1.53% vs 1.71% p=0.289	-	-
Drug discontinuation rate	21.2% vs 16.6%	20.7% vs 16.6%	25.3% vs 27.5%	23.9% vs 22.4%	-	-

AF: atrial fibrillation; DOACs: direct oral anticoagulants; NVAF: nonvalvular atrial fibrillation; SE: systemic embolism

Table 1.9 Patient characteristics comparison with contemporary AF registries

Patient characteristics	GARFIELD-AF (103) (n=10,614)	ORBIT-AF (104) (n=9957)	Fushimi AF Registry (105) (n=3183)	RecordAF (106) (n=5604)	Stockholm AF database (107) (n=43, 353)	J-RHYTHM (108) (n=7,937)	GLORIA-AF (109) (n=10,675)	Realise-AF (110) (n=10,523)	EORP-AF (111) (n=3049)	ORBIT-AF II (112)	ATRIUM (113) (n=3,667)
Age in years	70.2	75	74.2	66	-	69.7	71.0	66.6	68.8	73	72
Men (%)	56.8	58.0	59.3	57	56	68. 9	54.5	56.4	59.6	56	
Comorbidities (%)											
CHF	21.0	32.1	27.9	26 (n=5,600)	37.3	-	23.7	45.8	47.5	23	43
HTN	77.8	83.0	60.6	68 (n=5,601)	64.9	59.1	74.9	72.2	70.9	83	84
Prior stroke/TIA	14.4	15.0	21.8	6 (n=5,572) 4 (n=5,540)	24.1 (stroke/TIA /SE)	14	9.4	14.1	10.5	11	20
Diabetes	22	29.4	23.2	16 (n=5,600)	19.7	18.2	23.0	21.3	20.6	27	35
MI	-	16	6.4	9 (n=5,560)	-	-	10.5	-	44.8	34	-
History of bleeding	3.5	-	1.7%	-	-	-	5.7	-	5.9	-	-
PVD	7.0	-	-	3 (n=5,487)	34.1	-		-	11.2	-	-
Mean $CHADS_2$	1.9	-	2.09	-	-	1.7	-	-	-	2	2.2
Mean CHA_2DS_2-VASc	3.2	-	3.43	-	3.82	-	-	-	3.2		3.8
Mean HAS-BLED	-	-	-	-	-	-	1.4	-	1.4		-

AF: atrial fibrillation; CHF: congestive heart failure; HTN: hypertension; MI: myocardial infarction; PVD: peripheral vascular disease; SE: systemic embolism; TIA: transient ischaemic attack

Table 1.10 Summary of real-world studies relating to warfarin versus DOACs

Research group, year	DOACs	VKAs	Follow-up	Summary of bleeding and TE outcomes
Sorensen et al (98) (2011)	Dabigatran 110mg (n=1612) Dabigatran 150mg (n=1114)	VKA (n=49640)	August 22-December 31, 2011	• Increased risk of TE and bleeding with dabigatran among previous VKA users • With cautious interpretation, dabigatran use in VKA naive patients seemed safe.
Southworth MR et al (97) (2013)	Dabigatran	Warfarin	October 2010 to December 2011	• Bleeding rates associated with dabigatran was not higher than those with warfarin, a finding that was consistent with the results of RE-LY
Larsen et al (95) (2013)	Dabigatran (n=4,978)	Warfarin (n=8,936)	10.5 months	• Similar stroke/SE and major bleeding rates with dabigatran (both doses) compared with warfarin
Berger R et al (96) (2013)	Dabigatran (n=15)	Warfarin (n=123)	6 months	• Fewer ICH in patients receiving dabigatran than warfarin
Yap LB et al (99) (2015)	Dabigatran (n=500)	Warfarin (n=500)	315±280 days	• Similar rates of efficacy for outcomes of ischaemic CVA, and bleeding
Kodani E et al (114) (2016)	DOACs (n=923)	Warfarin (n=3,964)	5 years	• DOACs was identified as a potential beneficial for reducing event rates of all types in Japanese NVAF patients
Korenstra J et al (115) (2016)	Dabigatran (n=442)	Acenocoumarol (n=478)	2010 to 2013	• Dabigatran appeared to be as effective, but significantly safer than acenocoumarol

CVA: cerebrovascular accident; DOACs: direct oral anticoagulants; SE: systemic embolism; VKA: vitamin K antagonist

1.7 Underutilisation of antithrombotic therapy in AF

All contemporary guidelines recommend stroke prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke.(7, 16) Despite this recommendation, anticoagulation is underused in patients with AF.(116, 117) A recent review (118) has identified that suboptimal use of anticoagulants particularly in a patients with a high risk of stroke, is a persisting challenge despite the availability of DOACs. The Garfield registry which is a prospective, multicentre, international registry of patients newly diagnosed with AF, has shown OACs are used inappropriately in a large proportion of AF patients.(119) A systematic review by Ogilvie et al (116) has highlighted suboptimal treatment of high risk patients with AF. In the majority of the studies they reviewed, patients with AF and prior stroke or TIA were found undertreated with OACs. Consequently, underuse of antithrombotic therapy is associated with an increase in the rate of death and ischaemic events (stroke, TIA, or MI).

There could be multiple reasons for underuse of oral anticoagulation;(120-123) some of them include low levels of therapy initiation, and the narrow therapeutic margin (INR ratio 2-3 in NVAF) leading to low patient compliance.(121) Inconvenience (124) and physicians' concern over haemorrhage were found to be other main reasons for the underuse of antithrombotic therapy in AF.(125-127) In a systematic review by Neidecker (128) physician surveys revealed the factors for not prescribing warfarin to be risk of falls, dementia, short life expectancy, and history of bleeding. In a study by Margaret et al conducted to track longitudinal warfarin use using pharmacy and laboratory databases, (129) out of 4188 warfarin initiated patients, 26.3% of the subjects discontinued therapy within 1 year of after warfarin initiation. Most of the patients to do so were aged <65 years, patients with poorer anticoagulation control and patients with lower stroke risk ($CHADS_2$ score of 0 compared to

4 to 6). Another study, carried among 651 patients on OACs after ischaemic stroke observed a 22% discontinuation rate after 1 year. Bleeding was the main reason for discontinuation and 'patient request' or 'hassle to visit anticoagulation clinic' were explanations for others.(130) A recent study conducted among elderly patients in Germany also revealed that a considerable proportion of AF cases did not receive antithrombotic drugs in routine care.(131)

Physicians are reluctant to prescribe warfarin in elderly patients due to high risk of falls and risk of traumatic ICH, poor compliance, difficulty in monitoring, cognitive impairment and risk of interaction with multiple other drugs.(132, 133) These issues may underline possible explanations for the substantial underutilisation of VKAs in the elderly population. OAC therapy continues to be underutilised in older adults despite compelling evidence of benefits of stroke reduction in the corresponding age group. While the double impact of clearer guidance together with the advent of DOACs was expected to increase current use of OAC, greatly improving patient outcomes and thus reducing the burden of AF–related stroke, (134) a recent review has highlighted suboptimal OAC use in patients with AF and poor compliance with guidelines still persists despite transition to a new era of anticoagulation featuring DOACs.(118)

1.8 Potential use of DOACs: pros and cons

DOACs do have several advantages over warfarin, as shown in Table 1.11, in terms of stroke prophylaxis in AF. There are disadvantages, however, as discussed below. The limitations of DOACs must be taken into account when treating patients and prescribers should try to maintain vigilance to minimise adverse outcomes.

Table 1.11: Advantages and disadvantages of anticoagulants

	Advantages	Disadvantages	Relevance
Warfarin	Well-known drug Better patient adherence due to once daily dosing Antidotes available Indicated in valvular AF Low cost	Narrow therapeutic index Slow onset and offset of action Unpredictable pharmacokinetic/ pharmacodynamic effects Multiple drug and food interactions Bridging required during surgery Requires frequent INR monitoring	Close INR monitoring difficult in resource-limited settings
DOACs	Fast onset of action Fixed dosing Fewer drug and food interactions Stable therapeutic levels No regular monitoring required Shorter half-life Predictable pharmacokinetic/ pharmacodynamic effects Surgery without bridging Lower ICH risk compared to warfarin Dabigatran dialyzable due to low plasma protein binding Prothrombin time can be used to measure effect of rivaroxaban Anti-factor Xa can be used to measure effect of apixaban	Not indicated for patients with valvular AF Twice daily dosing (dabigatran and apixaban) Antidotes development in progress Dosage adjustment in renal impairment Lack of long term-safety data Gastrointestinal haemorrhage and MI risk (dabigatran) Laboratory monitoring tools unreliable Cost	Setting-specific AF management guidelines and further cost-effectiveness studies required

AF: atrial fibrillation; ICH: intracranial haemorrhage; INR: international normalised ratio; MI: myocardial infarction; DOACs: non-VKA-oral anticoagulants

1.8.1 Safety and efficacy issues

There are a range of safety and efficacy issues particularly relevant to prescribers when considering the place of DOACs in stroke prophylaxis in AF. The safety data generated by clinical trials is not enough to provide recommendations regarding the place of DOACs in real-world practice, or to suggest that they should replace warfarin therapy. However, given that warfarin therapy is sometimes poorly controlled, DOACs could have a wider safety margin as compared to warfarin. Hence, DOACs could potentially be assessed as an alternative to warfarin therapy taking into account safety, efficacy and cost-effectiveness issues prior to their introduction.

1.8.2 Ethnicity

It is recognised that ethnicity can influence the pathophysiology of disease, and therefore patient response to therapy.(135) A sub-analysis of RE-LY (136) conducted to identify the effects of dabigatran versus warfarin on ischaemic and haemorrhagic strokes and bleeding in Asian and non-Asian patients revealed haemorrhagic stroke rates were higher with warfarin in Asians versus non-Asians, despite similar blood pressure, younger age, and lower INR values. Haemorrhagic strokes were significantly reduced with dabigatran in both Asians and non-Asians. The benefits of dabigatran were consistent across Asian and non-Asian subgroups. These data are particularly reassuring for prescribers in Asian developing countries.

1.8.3 Short half-life

The short half-life of these drugs could make patients more prone to stroke or SE if doses are missed and not taken regularly. The short half-life of these drugs, along with the lack of routine coagulation monitoring measures and approved algorithms for the same, makes it difficult to ascertain with the DOACs if therapeutic failure is due to clinical causes (drug-drug interactions etc.) or patient nonadherence. Comprehensive patient counselling will play an important role in prevention and self-reporting of these adverse outcomes.

1.8.4 No routine coagulation monitoring required

The lack of a readily available assay to precisely measure the anticoagulation effect of the DOACs may be problematic. This is especially true in emergency situations, but also during chronic therapy. The short half-life of the DOACs makes strict adherence to therapy vital; patients are more prone to stroke or SE if doses are missed and not taken regularly. Unlike with warfarin, where regular INR monitoring provides objective evidence for assessing non-

adherence and the risk of thrombosis or bleeding-related outcomes, the lack of such regular monitoring with DOACs can potentially increase the risk of stroke or SE due to undetected poor drug adherence.

Furthermore, it has been observed that there is large variability in the plasma concentrations achieved with any given dose of dabigatran, depending on absorption, renal function, and other patient factors.(63, 137, 138) Variation in plasma concentration could potentially lead to under-response or over-response to dabigatran. This may hold true for other DOACs as well. A range of commercial assays, like the anti-Xa and chromogenic assays are in development but have not yet been approved. Measures like prothrombin time, thrombin time, activated partial thromboplastin time, ecarin clotting time, prothrombinase-induced clotting time, and modified prothrombin time are being used with varying degrees of success.(139-144) The monitoring limitations of the DOACs further emphasise the importance of the appropriate choice of drug and dose based on patient characteristics in an attempt to ensure optimal therapeutic benefits. Lack of monitoring tools can also be problematic in patients having comorbid conditions, such as renal disease, where dosage adjustments are required to optimise safety.

1.8.5 Reversal agents

Clinical trials have shown the bleeding profiles of DOACs, particularly ICH and haemorrhagic stroke, are better than that of warfarin. Furthermore, a recent review of five phase III trials comparing dabigatran with warfarin showed patients experiencing major bleeding on dabigatran required less intensive monitoring and had a lower mortality rate than those taking warfarin.(145) Nevertheless, specific guidelines are required for managing DOAC-related bleeding. Currently, the management of bleeding due to DOACs is based on

experts' opinions or laboratory endpoints, rather than on clinical experience.(146) Monoclonal antibodies against the DOACs and recombinant Xa-analog to reverse the factor Xa inhibitors are being investigated in clinical trials.(147) A humanised Fab fragment of a monoclonal antibody against dabigatran appears to give rapid and complete inhibition of its anticoagulant effect.(148)

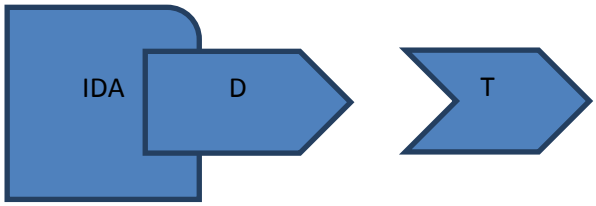
Idarucizumab is the first dabigatran-specific antidote. It is a humanised monoclonal antibody that binds specifically to dabigatran and has an affinity 350 times greater than thrombin.(149, 150) The REVERSAL Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD) study is an ongoing phase III trial, evaluating the reversal of the anticoagulant effects of dabigatran in patients who present with uncontrollable or life threatening bleeding or require emergency surgery or procedures.(150) The results of this trial found that idarucizumab completely reversed the anticoagulant effect of dabigatran in 88 to 98% of patients within minutes. The dabigatran associated anticoagulant reversal action of idarucizumab is shown in Figure 1.4A and 1.4B.(151)

Andexanet alfa is another antidote, currently studied to evaluate its safety and efficacy in reversing apixaban and rivaroxaban-induced anticoagulation in healthy volunteers in two parallel trials - Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R).(152) The trials concluded that andexanet can reverse the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects.

A

dabigatran bound thrombin is unable to participate in clotting function

B



Excreted in urine *Returns to clotting activity*

Figure 1.4A: dabigatran (D) thins the blood by binding to a specific clotting factor, thrombin (T), and preventing it from functioning normally. This lack of thrombin function thins the blood.
Figure 1.4B: idarucizumab (IDA) reverses the anticoagulation effect of dabigatran by binding to dabigatran with >350 times the strength with which dabigatran binds to thrombin (T). This leaves thrombin free to once again participate in the clotting process. The IDA-D complex then leaves the body in the urine.

1.8.6 Gastrointestinal bleeding

A recent meta-analysis (153) of 43 randomised controlled trials (151,578 patients) that compared DOACs with standard care has confirmed a 40-50% increase in the risk of GI bleeding associated with DOACs. The study defined standard care as low-molecular-weight heparin, VKA, antiplatelet therapy, or no (additional) therapy/placebo, depending on the guidelines regarding antithrombotic therapy for the relevant indication. Among the drugs studied, the OR values were: apixaban 1.23 (95% CI, 0.56-2.73), dabigatran 1.58 (95% CI, 1.29-1.93), edoxaban 0.31 (95% CI, 0.01-7.69) and rivaroxaban 1.48 (95% CI, 1.21-1.82). This highlights the importance of risk stratifying patients to identify individuals at increased risk of DOAC-related GI bleeding.

Using bleeding assessment tools like the HAS-BLED score (33) may help to identify patients at increased risk of GI bleeding before prescribing any anticoagulant therapy. This risk score was used to investigate predictors of bleeding in a cohort of patients with AF participating in the SPORTIF (Stroke Prevention using an Oral Thrombin Inhibitor in atrial

Fibrillation) III and V clinical trials.(35, 154-156) These trials included patients from different countries in Europe, Asia, and Australasia, suggesting the utility of this tool in developing, as well as in developed, countries. The analysis predicted diabetes and heart failure or left ventricular dysfunction as additional risk factors for bleeding.

1.8.7 Dose adjustments in chronic kidney disease (CKD)

As warfarin is not renally excreted, it can generally be used in patients with a creatinine clearance (CrCl) less than 30mL/min. Use of DOACs in renally impaired patients requires very close monitoring of the renal status of the patients to prevent overdose-associated toxicities with these drugs. Dose adjustments are recommended as renal function declines, and DOACs are contraindicated in stage 4 and stage 5 CKD as sufficient data on the use of DOACs in these patients are lacking.(157)

1.8.8 Switching between different anticoagulants

Proper evidence-based guidelines need to be formulated for effective antithrombotic therapy in patients with AF. Currently, switch-over practices between different antithrombotic drugs should be based on international guideline recommendations. Physicians should be familiar with basic pharmacological and pharmacokinetic properties of OACs to keep the switch-over practices safe (158), and ensure adequate crossover of agents and bridging when necessary.(158)

Switching from warfarin is advocated only if INR control has been poor or if frequent monitoring is problematic.(59) The findings of a recent study also suggest that caution should be adopted when shifting high-risk patients from VKA to dabigatran treatment.(98) The SAMe-TT_2R_2 score [sex (female), age (<60 years), medical history

(defined as more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease), treatment (interacting drugs, e.g., amiodarone for rhythm control), tobacco use (within 2 years), race (non-white)] (Table 1.12) aids decision-making for physicians by identifying patients with AF who are likely to do well on warfarin (score 0-1) or those who are more likely to have poor anticoagulation control (score >2).(159) Patients with a score greater than 2 could benefit from DOACs as initial therapy or alternatively be identified for use of more aggressive interventions for better anticoagulation control.(160) This could be a very useful tool to attempt to rationalise the use of DOACs, and ensure their receipt by those patients likely to obtain the most benefit from them.

Table 1.12 Definition of the SAMe-TT_2R_2 score

Acronym	Definitions	Point
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history	1
T	Treatment (interacting drugs e.g., amiodarone for rhythm control)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2
	Maximum points	8

1.8.9 Drug-drug interactions

Although DOACs have a much lower potential for drug-drug interactions (DDIs) than warfarin, they are not without risk. As with all OACs, concomitant use of other anticoagulants, platelet inhibitors or NSAIDs increases the risk of bleeding.(146) In addition, physicians need to consider the pharmacokinetic effects of accompanying drugs when prescribing DOACs.(146) Clinically relevant DDIs are known to result as dabigatran, rivaroxaban, and apixaban are substrates of P-glycoprotein (P-gp) and rivaroxaban and apixaban are metabolized by cytochrome P450 3A4 (CYP3A4).(161-163) Drugs that are administered concurrently to AF patients may have relevant activity against P-gp and/or CYP3A4, and thus may result in DDIs with DOACs. While prescribers may be familiar with the pharmacokinetic DDIs of warfarin, there may be relatively unfamiliarity with the DDIs of DOACs. Hence, clinicians should be aware of the relevant potential interactions with the P-gp and cytochrome P450 systems.(70, 157) Caution, possibly with a dose reduction for some of the DOACs, is recommended in patients on concomitant therapy with a strong P-gp inhibitor (e.g. amiodarone, verapamil and ketoconazole); while potent inducers such as rifampicin, carbamazepine or phenytoin may result in therapeutic failure and should not be administered concomitantly.

1.8.10 DOACs in patients with mechanical heart valves

The use of dabigatran in patients with mechanical heart valves has been associated with increased rates of TE and bleeding complications compared to warfarin (164-166), perhaps due to inadequate plasma dabigatran concentrations.(167, 168) Hence, the direct thrombin inhibitor dabigatran is contraindicated in patients with AF and a mechanical heart valve.(169) Information on safety and efficacy of other DOACs is lacking in this condition; guidelines suggest avoiding

other DOACs until more data is available.(6) Lack of usefulness of DOACs in this condition suggests the need for specific thromboprophylaxis guidelines, mindful of the needs of these patients.

1.8.11 Risk of MI

There exist significant differences in the comparative safety of apixaban, rivaroxaban and dabigatran with regards to acute coronary adverse events.(170) In the RE-LY study, dabigatran was associated with a significantly higher MI rate than warfarin (RR: 1.38 for dabigatran 150mg, P=0.048; RR: 1.35 for dabigatran 110mg, P=0.07).(66) A recent meta-analysis of randomized controlled trials investigating the risk of MI with the use of DOACs also suggested that they were associated with an increased risk of MI.(171) Overall, there is a lack of conclusive evidence to support the association between DOACs and MI, although some of the initial signals are of concern.(171) Prospective evaluation of the DOACs is expected to provide more convincing data regarding outcomes in real world practice.

1.8.12 Cost-effectiveness

Emerging evidence suggests that the new anticoagulants are cost-effective across a range of health settings with incremental cost-effectiveness ratios (ICERs) against warfarin ranging from $3,547 to $150,000 in different health care settings.(172) A recent review (173) concluded that the economic and clinical benefits of the DOACs, along with appropriate risk stratification, may enable a greater proportion of patients with AF to receive effective and convenient prophylaxis. In addition, several economic models have shown lowered rates of clinical events, increased patient survival and reduced cost of long-term disability with dabigatran therapy.(174-178) The

absolute cost of DOACs is significantly higher than the traditional agents, however, and this must be taken into account when formulating recommendations to ensure appropriate and equitable allocation of limited health care resources.(179) The preferred stroke prevention strategy should be carefully determined by the risk of stroke and ICH, quality of warfarin control and affordability. Hence, DOACs could be a better option where anticoagulation control with warfarin is not optimal. Although warfarin therapy is considered to be relatively inexpensive, the costs of frequent laboratory monitoring and of complications due to under-or over-anticoagulation are considerable.(180) DOACs have the potential to substantially reduce cost burden through improved efficacy, safety and ease of use compared with warfarin. Less stringent monitoring requirements that remove the burden of care from hospitals and clinics, fewer interactions, potential elimination of the need for induction and bridging, reduced education intensity and a more stable and consistent level of anticoagulation could minimise the overall costs associated with DOACs.(181) A recent review found that, on balance, evidence regarding the efficacy and safety of the DOACs suggests that they are a potentially cost-effective alternative to warfarin.(182) Nevertheless, the cost of the DOACs both to individuals, and the health care system, potentially remains the most significant barrier to patients in developing countries switching to DOACs.(183), A study that investigated the cost-effectiveness of five alternative AF management strategies (rivaroxaban, warfarin, aspirin plus clopidogrel, aspirin and no prevention) in a health-resource-limited setting of China concluded that although rivaroxaban can improve health outcomes compared with warfarin and antiplatelet-based strategies, it was not cost-effective at its current price.(179) The authors stated that, in resource-limited settings, a more pragmatic approach was to increase warfarin utilisation and, in particular, improve the quality of INR control.(179) Further studies comparing the cost-

effectiveness of DOACs and other strategies are required in other developing regions. An additional consideration is that the willingness to pay (WTP) per quality-adjusted life year (QALY) value is low in developing countries.(184, 185) Hence, the advantages of DOACs discussed so far may be outweighed by this lower WTP/QALY, resulting in warfarin being favoured in developing countries. It is thus evident that optimal prescribing of DOACs warrants the development of a model that takes into account budget assessment, communication programs with all key stakeholders, patient follow-up and adherence evaluation by authorities to better manage the entry of these agents into practice and to avoid their premature withdrawal and/or struggle for funding.(186) This principle unequivocally applies to resource-limited settings as an aid for their decision-making process in relation to DOACs.

The alternative approaches to improve existing anticoagulation therapy in resource limited settings include the use of point-of-care (POC) testing, warfarin-dosing-protocols, anticoagulation management services with dedicated personnel (i.e., anticoagulation clinics) and computer software programs to aid in dose adjustments.(187) Anticoagulation managed by anticoagulation clinics was found to give better outcomes and to be a cost-effective alternative compared to patients' managed by their personal physicians in China.(188) Similarly, POC measurement offers the potential for both simplifying and improving oral anticoagulation management in the professional setting as well as at home and has proven to be an effective monitoring modality.(187, 189-191) There is the potential that similar benefits could be observed in resource limited countries, especially in settings with poor access to pathology services.(189) Further research to assess the relative cost-effectiveness of these strategies compared to introduction of the DOACs would better inform appropriate allocation of health resources.

1.9 DOACs into clinical practice

DOACs have been approved for use in Australia and are widely available in the developed world. In countries where these drugs have not yet been introduced, prior to the introduction of DOACs, however, a model must be developed to aid in the decision-making process regarding the launch of these agents in a particular country. Making decisions that take cost-effectiveness of healthcare interventions into account, in addition to safety and efficacy, has become a genuine concern. Hence, the evaluation of the introduction of new drugs should consider safety, budget concerns and the quality of oral anticoagulation care achieved by each country. The choice between the available DOACs should be based on patient preferences, adherence, and ease of administration, as well as on local factors affecting cost-effectiveness.(192) Country-specific guidelines must be developed for the management of AF to aid clinicians in choosing the right NOAC for the right patient and at the right dose, and in performing the necessary follow-up and monitoring. VKAs may continue to have a role in selected patients or countries, especially if alternative monitoring strategies can be utilised. Ideally, prospective registries should be established in every country where feasible to investigate the comparative safety, efficacy and cost-effectiveness of DOACs and VKAs, to better define the roles of these agents into the future.

1.10 Rationale for the Tasmanian AF (TAF) study

Although antithrombotic therapy is essential for stroke prevention in AF, there is limited data on the pattern of use of these drugs in the Tasmanian population. The available literature suggested that there was underutilisation of anticoagulant therapy (193, 194), although this data come from relatively small observational trials in selected patient groups.(193, 195) The Commonwealth Review of Anticoagulation Therapies in AF in Australia identified that stroke prevention in

individuals with AF requires improvement, and highlighted a range of issues to be addressed related to the assessment of patients for stroke and bleeding risk, appropriate choice of antithrombotic agent(s) in patients with multiple comorbidities, and the monitoring of patients.(53) The review stressed the need for local data on which to base recommendations regarding the treatment of AF. Additionally, since there was also a lack of a contemporary, comprehensive Australian guideline for the management of AF to assist in decision-making process and to optimise outcomes, the review highlighted the need of national AF management guidelines. Meanwhile, little was known about the clinical outcomes and safety of DOACs outside the trial setting. In 2011, dabigatran's sponsor launched patient familiarisation program in which over 28,000 Australians were enrolled. Thus, the need of critical local data regarding the safety of antithrombotic medications, including the DOACs, in the treatment of AF and a comprehensive national guideline for the detection and management of AF was deemed necessary in Australia. This study aimed to contribute to the development of national guidelines for AF management in Australia with its explicit focus on rational use of antithrombotic therapy. The rationale behind this project was to derive local data on usage patterns of antithrombotic therapy, clinical outcomes and their safety profile in Australian sub-population prior to the Pharmaceutical Benefits Scheme (PBS) listing of DOACs and establish an ongoing study to monitor the prescribing and outcomes of stroke prevention in AF in a cohort of Australian patients.

We designed this study, the TAF Study, as a starting point to providing comprehensive data describing the outcomes of current stroke prevention strategies in Tasmanian patients with AF. The TAF study is an ongoing retrospective study that enrols patients from three different

hospitals in Tasmania, Australia; the Royal Hobart Hospital (RHH), Launceston General Hospital (LGH) and North West Regional Hospital (NWRH).

1.11 Aims and objectives

The main aims of this study were to retrospectively:

1) Review the patient characteristics and antithrombotic treatment patterns among patients with AF in Tasmanian hospitals,

2) Compare the anticoagulant utilisation to earlier data in the same population and identify predictors of anticoagulant prescribing among patients with NVAF,

3) Evaluate the rates of, and factors associated with, hospital readmissions due to bleeding or TE complications among patients newly diagnosed with AF, and

4) Compare the patient characteristics, antithrombotic prescribing patterns, and rates of bleeding or TE outcomes between older and younger patients diagnosed with AF.

Chapter 2

Chapter 2: Patient Characteristics and Antithrombotic Prescribing Patterns in Patients with Atrial Fibrillation in Tasmania

2 Abstract

Limited data are available on AF and its clinical management and outcomes from an Australian perspective. This study was designed to examine the patient characteristics and antithrombotic treatment patterns among patients with AF in Tasmania, Australia. This retrospective observational study reviewed and followed patients with AF admitted to Tasmania's three major hospitals between January 2011 and June 2012. Patients were excluded if they had only one episode of AF that reverted spontaneously or upon cardioversion without any documented recurrences. We reviewed the records of 2502 patients (≥ 18 years); 1469 were subsequently included in the study. The mean ± (SD) age of the patients was 76 ± (12.3) years. The mean (± SD) $CHADS_2$ score was 2.1 ± (1.3); 65.7% had a score ≥ 2. In total, only 55.6% of patients with $CHADS_2$ score ≥ 2 were receiving anticoagulation and 9.9% were not receiving any antithrombotic treatment, whereas 85.4% of those at low risk (score 0) were on antithrombotic therapy. Hospitalisation was associated with a significant increase in the rate of combination (antiplatelet plus anticoagulant) therapy ($P<0.001$). Suboptimal use of antithrombotic therapy highlights the need to improve AF management in our jurisdiction.

2.1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder and is increasing in incidence and prevalence in aging populations.(1) Studies indicate that 1.5-2% of the developed world population suffers from AF.(8) AF often coexists with hypertension (HTN), heart failure, coronary artery disease, and diabetes mellitus, (196) and increases the risk of mortality and morbidity, particularly due to stroke or thromboembolism (TE).(11)

Studies have provided details of the characteristics, risk profiles, management, and clinical outcomes of patients with AF.(103, 197) Although all contemporary guidelines recommend prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke, (7, 16) there have been consistent reports of underuse of anticoagulation, as well as overuse in low risk patients.(103, 198) For instance, the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Pilot Survey revealed that antiplatelet therapy was still being overprescribed, with or without anticoagulation, while elderly patients were commonly undertreated with oral anticoagulation despite their high risk of stroke and thromboembolic complications.(197)

At present there are limited data available on the characteristics, clinical management and outcomes of patients with AF from an Australian perspective. The available literature suggests that there is underutilisation of anticoagulant therapy, (193, 194) although this data comes from relatively small observational trials in selected patient groups.(193, 195) The Commonwealth Review of Anticoagulation Therapies in AF in Australia identified that stroke prevention in individuals with AF requires improvement, and highlighted a range of issues to be addressed

related to the assessment of patients for stroke and bleeding risk, appropriate choice of antithrombotic agent(s) in patients with multiple comorbidities, and the monitoring of patients.(53) The review stressed the need for local data on which to base recommendations regarding the treatment of AF. We designed this study, the Tasmanian AF (TAF) Study, as a starting point to providing comprehensive data describing the outcomes of current stroke prevention strategies in Tasmanian patients with AF. The aim of the current paper is to describe the characteristics of patients with AF admitted to three different Tasmanian hospitals and the appropriateness of antithrombotic prescribing patterns according to existing guideline recommendations.

2.2 Materials and Methods

2.2.1 Study design

Patients were identified by the Medical Record Departments at the Royal Hobart Hospital (RHH), Launceston General Hospital (LGH) and North West Regional Hospital (NWRH). The RHH is a 500-bed hospital servicing the southern region of Tasmania, Australia (population of 255,614). The LGH is a 300-bed hospital servicing residents of Launceston and the northern region of Tasmania (population of 143,544). Similarly, the NWRH is a 160-bed hospital providing services to North West Tasmania and King Island (population of 114,001).(199)

We reviewed medical records (admissions between 1st January 2011 and 30th June 2012) of 2502 patients aged $\geq$ 18 years with a diagnosis of AF (both valvular and non-valvular) at discharge (Australian Refined Diagnosis Related Group (AR-DRG) code I48: atrial fibrillation or flutter). Patients diagnosed with AF as their primary (i.e. AF was the presenting complaint) or

secondary condition (i.e. AF was listed as a current illness in the medical history or discharge summary) were included. Patients were excluded if they had only one episode of AF that reverted spontaneously or upon cardioversion without any documented recurrences, as stroke prophylaxis may not be warranted in these patients. Contraindications (CIs) to anticoagulant therapy included a history of dementia, documented labile INR, bleeding disorders, or allergies to anticoagulant therapy, and breastfeeding or pregnancy in women. We considered a patient's index admission as their first admission within our data collection period with a diagnosis of AF that met the study's inclusion criteria.

Data collected at baseline (i.e. at each patient's index admission) included patient demographics, medications on admission, documented previous medical history, relevant laboratory data, discharge diagnosis and discharge medications. The $CHADS_2$ and CHA_2DS_2-VASc risk assessment scores were used to estimate stroke risk. The $CHADS_2$ score was derived by allocating one point each for CHF, HTN, age ≥75 years and diabetes, and two points for previous stroke or TIA.(17) The CHA_2DS_2-VASc score was calculated by assigning one point each to CHF, HTN, diabetes, vascular disease (prior MI, peripheral artery disease or aortic plaque), age 65-74 years and female gender, and two points for age ≥75 years and previous stroke or TIA or TE.(20) A $CHADS_2$ score of 0 was considered low risk, 1 intermediate risk and ≥2 high risk; while a CHA_2DS_2-VASc score of 0 represented low risk and ≥1 was considered intermediate-high risk. The HAS-BLED score was used to estimate bleeding risk assessment. It was derived by allocating one point each for HTN, abnormal renal function, abnormal liver function, bleeding pre-disposition, age >65 years, labile INRs (if documented), the use of drugs predisposing patients to bleeding (NSAIDs), alcohol use (>8 drinks per week) and previous

stroke.(33) A HAS-BLED score of 0 indicated low risk, 1-2 indicated intermediate risk and ≥ 3 indicated high risk. Even though the CHA_2DS_2-VASc and HAS-BLED scores were not available to clinicians to guide treatment during the study time period, they were included in the analysis to assist in interpretation of our results. The Charlson Comorbidity Index (CCI) was used as a measure of comorbidity.(200)

Our 'antiplatelet' group consisted of patients receiving aspirin, clopidogrel, prasugrel, dipyridamole or ticagrelor either alone or in combination with each other but not in combination with an anticoagulant. The 'lone anticoagulant' group consisted of cases receiving warfarin, dabigatran, heparin, fondaparinux or enoxaparin. Patients taking a combination of an anticoagulant with an antiplatelet agent constituted the 'combination therapy' group. Finally, patients receiving any one of these drug groups were considered to be on antithrombotic therapy i.e. either on antiplatelet or anticoagulant or on combination therapy. We utilised the recommendations from the European Society of Cardiology (ESC) 2010 guidelines and American College of Chest Physicians (ACCP) 9th edition, (7, 16) to examine the appropriateness of antithrombotic prescribing at discharge of the index admission. We considered underutilisation as non-prescribing of anticoagulation, with or without antiplatelet therapy, to patients without documented CIs to anticoagulant therapy and a $CHADS_2$ score ≥ 2 as per these guidelines.

2.2.2 Statistical analysis

Data were analysed using SPSS version 21 (Prentice Hall, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as

frequencies and percentages. Differences between cohorts were tested for statistical significance using Mann-Whitney U and Chi-square tests, as appropriate. $P<0.05$ was considered as statistically significant for all analyses.

Ethics approval for the project was obtained from Tasmanian Health and Medical Human Research Ethics Committee.

2.3 Results

2.3.1 Baseline characteristics

The medical records of 2502 patients were reviewed, of whom 1469 were included (RHH: 777, NWRH: 289, LGH: 403) and 1033 were excluded (episode of AF that reverted spontaneously or upon cardioversion: 590, developed AF as a short-term complication: 288, no documented AF [coding error]: 155). The mean ± (SD) age of the included patients was 76 ± (12.3) years; 55.6% were male. Valvular AF was observed in 11.3% (166) of patients. HTN was the most commonly associated comorbid condition (65.7%). The demographics and clinical characteristics of the patients are summarised in Table 2.1.

The mean ± (SD) $CHADS_2$ score was 2.1 ± (1.3), and 65.7% had a score ≥2. The mean ± (SD) CHA_2DS_2-VASc score was 3.7 ± (1.7); 8.2% had a score of 1, while 88.6% had a score ≥2. The majority of the patients (73.5%) had an intermediate HAS-BLED score of 1-2, as shown in Table 1. A CI to antithrombotic treatment was documented in 9.9% of patients.

Table 2.1 Baseline characteristics of patients enrolled in TAF study

Variables	All patients (n=1469)
Age in years, Mean (SD)	76.0 (±12.3)
Age group, n (%)	
≥65	1249 (85.0)
≥75	878 (59.7)
≥80	628 (42.7)
≥85	325 (22.1)
Men, n (%)	817 (55.6)
Medical history, n (%)	
Hypertension	965 (65.7)
Ischaemic heart disease	509 (34.6)
Congestive heart failure	377 (25.7)
Chronic respiratory disease	374 (25.5)
Diabetes	310 (21.1)
Cerebrovascular disease	295 (20.1)
Myocardial infarction	238 (16.2)
Embolic events (DVT, Pulmonary embolism)	109 (7.4)
Peripheral vascular disease	90 (6.1)
History of bleeding	37 (2.5)
Valvular heart disease, n (%)	166 (11.3)
AF history, n (%)	
First detected AF	387 (26.3)
Previous AF	1082 (73.6)
CCI (classic), Mean (SD)	5.3 (±2.4)
$CHADS_{2,}$ Mean (SD)	2.1 (±1.3)
Low (score 0)	153 (10.4)
Intermediate (score 1)	350 (23.8)
High (score 2-6)	966 (65.7)
CHA_2DS_2-VASc, Mean (SD)	3.7 (±1.7)
Low (score 0)	45 (3.1)
Intermediate (score1)	121 (8.2)
High (score 2-9)	1303 (88.6)
HAS-BLED, Mean (SD)	1.8 (±0.8)
Low (score 0)	93 (6.3)
Intermediate (score1-2)	1079 (73.5)
High (score ≥3)	297 (20.2)
Antithrombotic therapy (on admission), n (%)	
Antiplatelet therapy	578 (39.3)
Anticoagulant therapy	463 (31.5)
AP/AC combination	101 (6.8)
No antithrombotic therapy	327 (22.2)
Other medications, n (%)	
PPIs	551 (37.5)
H2Bs	40 (2.7)
Statins	661 (45.0)
Prednisolone	149 (10.1)
NSAIDs	83 (5.7)
Reason for index admission, n (%)	
Related to AF	390 (26.5)

Variables	All patients (n=1469)
Bleeding	63 (4.3)
Thromboembolism	189 (12.9)
Other cardiovascular conditions	258 (17.6)
None of the above	569 (38.7)

AP/AC: antiplatelet and anticoagulant; AF, atrial fibrillation; CCI, Charlson comorbidity index; DVT, deep vein thrombosis; H_2Bs, histamine-2 receptor blockers; PPIs, proton pump inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation.

2.3.2 Thromboprophylactic treatment

Based on ACCP 9th edition and ESC 2010 guidelines, (7, 16) 64.1% (n=808) of the 1261 patients with no documented CIs to antithrombotic therapy had a $CHADS_2$ score ≥ 2 and were therefore eligible for anticoagulant therapy (Table 2.2). An anticoagulant was prescribed for 55.6% (n=449) of these patients at discharge. These percentages were broadly similar for the intermediate risk ($CHADS_2$=1) group. Antiplatelet agents were prescribed in an additional 34.5% (n=279) of patients. Eighty (9.9%) patients with a $CHADS_2$ score ≥ 2 were not receiving any antithrombotic therapy. "Physician decision" was the only documented reason for not prescribing antithrombotic therapy (n=34, 3.0%), despite patients having intermediate to high risk of stroke ($CHADS_2$ score $\geq$1) without any CIs. In contrast, 85.4% (n=123/144) of patients in whom no treatment may have been indicated due to their low risk of stroke ($CHADS_2$=0) were receiving antithrombotic therapy. Only 5.6% (n=8/144) of these patients had an embolic disease history other than AF and therefore alternative indications for anticoagulation. Furthermore, among those receiving lone antiplatelet agents and having a $CHADS_2$=0, 16.3% (8/49) had a history of ischaemic heart disease (IHD).

Similar findings arose when prescribing was evaluated against patients' CHA_2DS_2-VASc scores. In this case, 96.9% (n=1222/1261) of patients with no CIs to antithrombotic therapy had

at least one additional risk factor for stroke and were therefore eligible for anticoagulant therapy (Table 2.2). An anticoagulant was prescribed for 57.0% (n=697/1222) of these patients. Antiplatelet agents were prescribed in 33.1% (n=405).

In assessing if anticoagulant underuse was associated with a high HAS-BLED score, we observed that 22.0% (n=278/1261) of patients without any CIs had a HAS-BLED score which exceeded their $CHADS_2$ score. Of these patients, 56.5% were on anticoagulant therapy, 34.9% on antiplatelet therapy, and 8.6% receiving no therapy, which was largely consistent with the overall population.

Table 2.2 Use of antithrombotic therapies, overall and according to $CHADS_2$ and CHA_2DS_2-VASc scores on discharge (excludes those with contraindications and those for whom no information was available, n =1261)

$CHADS_2$ scores	Antiplatelet therapy (%)[a]	Anticoagulant therapy (%)[b]	Combination therapy (%)[c]	Any Antithrombotics (%)[d]	No therapy (%)
$CHADS_2$ =0 (n=144)	49 (34.0)	56 (38.9)	18 (12.5)	123 (85.4)	21 (14.6)
$CHADS_2$ =1 (n=309)	90 (29.1)	130 (42.1)	61 (19.7)	281 (90.9)	28 (9.1)
$CHADS_2$ ≥ 2 (n=808)	279 (34.5)	307 (38.0)	142 (17.6)	728 (90.0)	80 (9.9)
Total (n=1261)	418 (33.1)	493 (39.1)	221 (17.5)	1132 (89.8)	129 (10.2)
CHA_2DS_2-VASc scores	**Antiplatelet therapy (%)[a]**	**Anticoagulant therapy (%)[b]**	**Combination therapy (%)[c]**	**Any Antithrombotics (%)[d]**	**No therapy (%)**
CHA_2DS_2-VASc =0 (n=39)	13 (33.3)	14 (35.9)	3 (7.7)	30 (76.9)	9 (23.1)
CHA_2DS_2-VASc ≥1 (n=1222)	405 (33.1)	479 (39.2)	218 (17.8)	1102 (90.2)	120 (9.8)
Total (n=1261)	418 (33.1)	493 (39.1)	221 (17.5)	1132 (89.8)	129 (10.2)

[a] The antiplatelet only group consisted of cases receiving aspirin, clopidogrel, prasugrel, dipyridamole, ticagrelor either alone or in combination with each other but not in combination with anticoagulants.

[b] The anticoagulant group consisted of cases receiving warfarin, dabigatran, heparin, fondaparinux and enoxaparin.

[c] The combination of an anticoagulant with an antiplatelet constituted the combination therapy group.

[d] Total antithrombotic therapy in each category

Of the patients without CIs, 11.4% (144/1261) had valvular AF. Among these patients, 54.9% were prescribed lone anticoagulant therapy, followed by combination therapy (23.6%), and 15.3% were taking antiplatelet monotherapy. The prescribing pattern of antithrombotic therapy differed significantly between the patients with valvular and nonvalvular AF, with higher rates of prescribing of lone anticoagulant therapy (54.9% vs. 37.1%, P<0.001) and combination therapy (23.6% vs. 16.7%, P<0.001), and a correspondingly lower rate of lone antiplatelet therapy (15.3% vs. 35.6%, P<0.001).

We also observed a significant difference in the prescribing pattern of combination antithrombotic regimens between the patients who were newly initiated (i.e. started antithrombotic therapy during the index admission) and continuing therapy (i.e. those on antithrombotic treatment prior to their index admission). A larger proportion of newly initiated patients were prescribed combination antithrombotic therapy (25.8% vs. 18.0% for the continuing group; P<0.001). Recent diagnosis of acute coronary syndrome (ACS), as a potential indication for combination therapy, did not seem to have increased its prescribing between these groups, with 4.0% of those newly initiated and 4.5% of those continuing on antithrombotic therapy diagnosed with ACS during their index admission (P=0.71).

2.3.3 Impact of hospitalisation on antithrombotic prescribing

When the antithrombotic prescribing patterns on admission and discharge were compared among the 693 patients who had a pre-existing AF continuing on antithrombotic treatment, significant changes were observed, with a reduction in the prescribing of lone antiplatelet (40.8% vs. 33.5%, P<0.001) and anticoagulant therapy (49.2% vs. 47.5%, P<0.001), and an increased rate of use of

combination therapy (10.0% vs. 18.9%, P<0.001) (Table 2.3). Only 4.0% of those with pre-existing AF continuing on antithrombotic therapy were diagnosed with ACS during their index admission.

Table 2.3 Antithrombotic therapy change associated with hospitalisation (only patients with pre-existing AF continuing on ATT, n=693)

	Admission			Discharge		
$CHADS_2$ score at admission	Antiplatelet[a]	Anticoagulant[b]	Combination[c]	Antiplatelet[a]	Anticoagulant[b]	Combination[c]
$CHADS_2 = 0$	31	27	2	26	27	7
(n=60)	(51.7)	(45.0)	(3.3)	(43.3)	(45.0)	(11.7)
$CHADS_2 = 1$	67	86	17	43	85	42
(n=170)	(39.4)	(50.6)	(10.0)	(25.3)	(50.0)	(24.7)
$CHADS_2 \geq 2$	185	228	50	164	217	82
(n=463)	(40.0)	(49.2)	(10.8)	(35.4)	(46.9)	(17.7)
TOTAL (n=693)	283	341	69	232	329	131
	(40.8)	(49.2)	(10.0)	(33.5)	(47.5)	(18.9)

[a] The antiplatelet only group consisted of cases receiving aspirin, clopidogrel, prasugrel, dipyridamole, ticagrelor either alone or in combination with each other but not in combination with anticoagulants. [b] The anticoagulant group consisted of cases receiving warfarin, dabigatran, heparin, fondaparinux and enoxaparin. [c] The combinations of an anticoagulant with an antiplatelet constituted the combination therapy group. Therapy changes: Antiplatelet: P<0.001*, Anticoagulant: P<0.001*, Combination: P<0.001*.

2.4 Discussion

Observational studies can be valuable in evaluating disease state management and its outcomes in a population, especially in countries like Australia which lack effective large-scale healthcare data linkage systems. The TAF study, an ongoing observational study of adults with AF, aims to comprehensively evaluate the management and outcomes of patients with AF. This paper provides a salient snapshot of AF management patterns among patients with AF who experienced a hospital admission in three Tasmanian hospitals during 2011 and 2012. In this large study of patients with AF we noted that, despite the high risk of stroke and thromboembolic complications, anticoagulant therapy was sub-optimal.

As our patient population was identified during hospital admission, it is perhaps unsurprising that they demonstrated high rates of comorbid conditions, especially cardiovascular diseases. Nevertheless, their characteristics proved to be largely similar to those of the populations studied in the Stockholm AF database, Fushimi AF Registry and ORBIT-AF Registry.(105, 107, 201) They were noted to be older and at higher risk of stroke compared to the GARFIELD study population, (103) but as GARFIELD is enrolling only patients with new onset AF, it is expected that this will have a younger, lower-risk cohort. The retrospective cohort of the TAF Study also compares well to the patient cohorts studied in clinical trials comparing NOACs to warfarin, in terms of mean age (76 vs. 70-73 years) and stroke risk (mean $CHADS_2$ 2.1 vs. 2.1-3.5).(66, 71, 74, 76) This suggests that our patient population is broadly comparable to that of other countries and to those studied in recent pivotal trials, indicating the likely transferability of international guidelines and the benefits indicated by these trials' results to our population.

Antiplatelet and anticoagulant therapies are available for stroke prevention in AF. Use of anticoagulation therapy for stroke prevention in AF is well accepted, established and recommended widely.(3) All contemporary guidelines recommend prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke, (7, 16) however discordance between AF guideline recommendations and anticoagulant prescribing patterns has been reported in various international studies.(103, 202)

In our study, despite the high risk of stroke observed (64.1% of patients had a $CHADS_2$ $\geq$2, and 96.9% had a CHA_2DS_2-VASc score of 1 or more), anticoagulant therapy was found to be underutilised according to guideline recommendations.(7, 16) At discharge from hospital, almost 10% of patients with a $CHADS_2$ $\geq$2 and CHA_2DS_2VASc score $\geq$1 were not taking any antithrombotic medication and approximately one-third were prescribed antiplatelet monotherapy. Given the time frame of our study and the guideline recommendations (16) during that time, $CHADS_2$ was the more realistic tool for assessing appropriateness of therapy in relation to estimated stroke risk; however, we have presented the results using both $CHADS_2$ and CHA_2DS_2-VASc scores believing that physicians might have also considered the additional risk factors subsequently included in CHA_2DS_2-VASc score.

This underutilisation of anticoagulant therapy in AF patients at relatively high risk of stroke is consistent with previous findings, (194, 203) with many clinicians considering the risk of anticoagulant treatment to exceed the benefits, when in fact those at higher risk of stroke often receive the greatest benefit from anticoagulation.(204) The potential risk of bleeding is one of the most frequent reasons of anticoagulant underuse among treating physicians.(205) Since

22.0% of our patients without any CIs had a HAS-BLED score which exceeded their $CHADS_2$ score, this might have contributed to the observed underutilisation of anticoagulant therapy. Given that the majority of our patient population were elderly and had multiple comorbidities, this might have led to physicians being more reluctant to prescribe anticoagulant therapy. A history of anaemia, history of hospitalisation/emergency room visits, older age, comorbidities, risk of falls, and previous bleeding have all been identified as reasons for non-prescribing of anticoagulants.(46, 103, 133, 206) The belief that antiplatelet therapy alone is sufficient for stroke prevention and/or lack of awareness of guideline recommendations (194) may also have contributed to the underutilisation of anticoagulant therapy. Nevertheless, the overall use of antithrombotic treatment seems to have improved since 1997-1999, when a study conducted among 505 patients diagnosed with AF at the RHH found that 24% of patients at high-risk were discharged without any antithrombotic therapy.(193)

Over 80% of the patients with a $CHADS_2$ score of 0, who are considered to be 'low-risk' patients, were receiving antithrombotic drugs at discharge. Nearly 40% of these patients were on anticoagulants; this overuse pattern is very similar to that found in the GARFIELD study (38.7%).(103) Other indications apart from AF might have justified the use of anticoagulants in some of these patients; however, only 5.6% had a history of embolic disease and data regarding other possible indications was not collected within the confines of this study. Similarly, a history of IHD among those with a $CHADS_2$ score of 0 (16.3%) might have made some patients eligible for antiplatelet therapy despite being at a low risk of stroke.

The final issue of concern raised by our data was the relatively high rate of prescribing of combination anticoagulant/antiplatelet therapy; this rate was especially high in patients newly initiated on therapy, and also increased from admission to discharge in patients with existing AF. One explanation for this prescribing pattern may be the diagnosis of a compelling guideline-recommended indication for antiplatelet therapy (e.g. ACS) in patients requiring anticoagulation for AF thromboprophylaxis.(16) ACS was only diagnosed among 4.0% of those with old AF continuing on antithrombotic therapy during the index admission in our study, however, so this is unlikely to have been a major influencing factor. Other potential reasons for the prescribing of a combination therapy may have been the use of antiplatelet agents as 'bridging therapy' during anticoagulant initiation or inappropriate failure to cease antiplatelet therapy upon initiation of anticoagulation. This issue warrants further investigation as combination therapy is associated with a significantly higher risk of bleeding.(16)

There is clearly an evidence to practice gap in guideline adherence to rational prescribing of antithrombotic regimens in patients with AF in our population. Local guidelines and other contextual factors may influence anticoagulant prescribing.(194) At present, there are no up-to-date Australian guidelines for the management of AF; thus, international guidelines are the basis of its management, and data regarding predictors of antithrombotic prescribing among patients with AF are as yet limited in Australia. The absence of robust national AF management guidelines might have influenced underutilisation or overutilisation of anticoagulant therapy in our population. Intervention programs, such as described previously, (207, 208) may be required to assist with optimising guideline concordance and therefore the proportion of Australian patients receiving appropriate thromboprophylaxis for stroke prevention in AF.

2.5 Conclusions

Our study highlights a gap between the evidence-based risk stratification and antithrombotic management pattern among patients with AF in Tasmania. In the absence of contemporary local guidelines, there appears to be a need to better support prescribers to assist in the identification and quantification of patient risk according to accepted international guidelines to optimise thromboprophylaxis and reduce the risk of thromboembolic and bleeding complications in this vulnerable patient group.

Chapter 3

Chapter 3: Anticoagulant use in Patients with Non-valvular Atrial Fibrillation: has prescribing improved?

3 Abstract

Discordance between international guideline recommendations and anticoagulant prescribing patterns among patients with non-valvular atrial fibrillation (NVAF) has been frequently reported. This study was designed to compare the anticoagulant utilisation pattern to earlier data in the same population, and identify predictors of anticoagulant prescribing among patients with NVAF. We reviewed patients with NVAF admitted to Tasmania's three major hospitals between January 2011 and June 2012 and compared the anticoagulant utilisation pattern to earlier data. Patients were excluded if they had only one episode of NVAF that reverted spontaneously or upon cardioversion. Multivariate logistic regression analysis was used to identify predictors of anticoagulant prescribing. Overall, 53.8% of patients received anticoagulant treatment compared to 40.4% 15 years ago. Among eligible patients at high-risk of stroke, 52.5% were receiving anticoagulant therapy (vs. 42.1% 15 years ago). Approximately 10% of patients with a $CHADS_2$ score ≥ 2 were not receiving any antithrombotic treatment, reduced from 18.2% in the earlier cohort, whereas anticoagulant use increased among those at low risk (score 0) to 48.5% from 14.2%. Younger age (odds ratio [OR] 0.99, 95% CI 0.97-1.0; P=0.04), $CHADS_2$=1, relative to 0 (OR 1.68, 95% CI 1.07-2.63; P=0.02), CHF (OR 1.56, 95% CI 1.12-2.15; P=0.008) and embolic disease history (OR 1.77, 95% CI 1.09-2.86; P=0.02) were significant predictors of anticoagulant prescribing. While there has been improvement over the past 15 years, suboptimal use of anticoagulant therapy among high-risk patients with NVAF remains common. There is significant potential for improvement in the quality of stroke prophylaxis in patients with NVAF.

3.1 Introduction

Long-term use of anticoagulant therapy is an important strategy in the management of NVAF and its efficacy for stroke prevention in this condition is well established.(3) Vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs) can be used for thromboprophylaxis. In comparison, antiplatelet therapy has limited utility for preventing stroke in AF.(7, 79) Despite the proven benefits of anticoagulant therapy in atrial fibrillation (AF), there have been frequent reports of discordance between guideline recommendations and anticoagulant prescribing patterns.(103, 202) Early discontinuation and underuse of anticoagulants in real-world practice have been reported.(46, 103, 133, 206) A retrospective study conducted by Jackson et al. 15 years ago (1997-1999) in Tasmania revealed that anticoagulant therapy was underused in high-risk patients with AF.(193) This study provided local data on stroke prophylaxis measures in AF at a particular point of time and provided the basis for an intervention to improve anticoagulant prescribing. In fact, a community-based educational intervention carried out among general practitioners, resulted in a significant increase in the prescribing of warfarin for stroke prevention in Tasmanian patients with AF.(209)

Contemporary guidelines recommend prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke.(7, 16) The guidelines recommend using risk stratification schemes, like $CHADS_2$ (17) or CHA_2DS_2-VASc, (20) to assess the risk of stroke in patients with AF prior to commencing antithrombotic treatment. Despite these guidelines, high-risk of stroke has not been found to be an independent predictor of anticoagulant prescribing in several observational studies.(210, 211)

Data regarding predictors of anticoagulant prescribing among patients with AF are limited in the Australian context. A prospective study conducted across a local health district in Sydney (194) revealed that the likelihood of receiving anticoagulant therapy among patients with NVAF increased by being classified at high-risk of stroke. Another study, involving a single hospital site revealed that patients aged 80 years or more were less likely to be prescribed anticoagulation compared to antiplatelet therapy.(207) The need to bridge the gap in translation of evidence into clinical practice was deemed necessary in both of these studies. We thus designed this study to determine i) the pattern of anticoagulant utilisation, compared with guideline recommendations, (7, 16) and predictors of anticoagulant prescribing in patients with NVAF and ii) whether stroke prevention in the management of patients with NVAF had improved over the past 15 years in Tasmania.

3.2 Materials and Methods

3.2.1 Study design

The TAF (Tasmanian Atrial Fibrillation) study is an ongoing retrospective study that enrols patients from three different hospitals in Tasmania, Australia; the Royal Hobart Hospital (RHH), Launceston General Hospital (LGH) and North West Regional Hospital (NWRH). We identified patients from the Medical Record Departments of these hospitals using Australian Diagnosis Related Groups (AR-DRGs) codes. Medical records of 2502 patients admitted between 1st January 2011 and 30th June 2012 and diagnosed with valvular or NVAF at discharge (AR-DRG code I48: atrial fibrillation or flutter) were reviewed for this study. Patients diagnosed with AF as their primary (i.e. AF was the presenting complaint) or secondary condition (i.e. AF was listed as a current illness in the medical history or discharge summary) were included. Patients were

excluded if they had only one episode of AF that reverted spontaneously or upon cardioversion without any documented recurrences, as stroke prophylaxis may not be warranted in these patients. Of 2502 medical records reviewed, 1469 patients were included (RHH: 777, NWRH: 289, LGH: 403) and 1033 were excluded (episode of AF that reverted spontaneously or upon cardioversion: 590, developed AF as a short-term complication: 288, no documented AF [coding error]: 155). Seventy-eight (5.3%) index admissions were excluded due to death of the patient or unavailability of their records, leaving 1391 patients. Of these, 1261 patients were eligible for anticoagulant therapy (i.e. did not possess contraindications (CIs)). After excluding 144 (11.4%) patients with valvular AF, 1117 patients with NVAF were included in this analysis.

Data regarding patient demographics, medications on admission, history of comorbid conditions and discharge antithrombotic medications were entered into an electronic database. The CCI (200) was used as a measure of comorbidity. We evaluated $CHADS_2$ (17) [congestive heart failure (CHF), hypertension (HTN), age ≥75 years, diabetes and previous stroke or transient ischaemic attack (TIA)], and CHA_2DS_2-VASc (20) [CHF, HTN, diabetes, vascular disease (prior myocardial infarction (MI), peripheral artery disease or aortic plaque), age 65-74 years, female gender, age ≥75 years and previous stroke or TIA or thromboembolism (TE)] for assessing stroke risk and the HAS-BLED (33) [HTN, abnormal renal function, abnormal liver function, bleeding pre-disposition, age >65 years, the use of drugs predisposing patients to bleeding (NSAIDs), alcohol use (>8 drinks per week), previous stroke and labile INRs (if documented)] score for assessing bleeding risk. A HAS-BLED score of 0 indicated low risk, 1-2 indicated intermediate risk and ≥ 3 indicated high risk. We defined labile INRs as unstable/high INRs as recorded in the medical record of our patients. A patient's first admission to a hospital

with the diagnosis of AF within our study period was defined as the index admission. CIs to anticoagulant therapy included patients with a documented history of dementia, labile INRs, bleeding diseases, allergies to anticoagulant therapy, and pregnancy.

Our definition of anticoagulant therapy for this study comprised anticoagulant therapy, with or without concomitant antiplatelet therapy. We utilised the recommendations from the European Society of Cardiology (ESC) 2010 guidelines and American College of Chest Physicians (ACCP) 9th edition,(7, 16) to examine the appropriateness of anticoagulant prescribing at discharge of the index admission. We considered underutilisation as no prescribing of anticoagulant therapy to patients without CIs to anticoagulant therapy and a $CHADS_2 \geq 2$ as per these guidelines. CHA_2DS_2-VASc scores were not available to clinicians to guide treatment during our data collection period. We also compared the changes in anticoagulant prescribing patterns referring to a local study conducted by Jackson et al. (1997-1999), 15 years ago in Tasmania.(193) This study was a retrospective review of 505 patients with NVAF admitted to RHH. The appropriateness of antithrombotic therapy was assessed both on admission and discharge from the hospital care, and sufficient data was available to calculate the $CHADS_2$ scores retrospectively. The study also determined the clinical outcomes (ischaemic stroke, SE or bleeding complications with warfarin or aspirin use) in the total population.

3.2.2 Statistical analysis

Data were analysed using SPSS version 21.0 (Prentice Hall, USA). Continuous variables were expressed as median (IQR). Categorical variables were expressed as frequencies and percentages. Chi square tests were used to compare categorical variables while Mann-Whitney U

tests were used for continuous variables. Multivariate logistic regression modelling was used to identify the independent risk factors associated with anticoagulant prescribing in eligible patients. Variables which had $P \leq 0.2$ in univariate analyses were combined in a multivariate logistic regression model (enter method). $P<0.05$ was considered as statistically significant for all analyses.

Ethics approval for the project was obtained from Tasmanian Health and Medical Human Research Ethics Committee. As the study was retrospective prescribing audit, it was not deemed necessary to ask for informed consent from the study participants.

3.3 Results

3.3.1 Clinical characteristics

The overall rate of anticoagulant use at discharge from the index admission among eligible patients was 53.8%. Characteristics of the patients anticoagulated, and not anticoagulated, at discharge are shown in Table 3.1. Patients treated with anticoagulants were significantly younger, likely to be male, have previously diagnosed AF, and more likely to have CHF and a history of embolic events.

Table 3.1: Baseline characteristics of patients with NVAF anticoagulated and not anticoagulated at discharge from index admission (n=1117)

Variable	Anticoagulated (n=601)	Not anticoagulated (n=516)	P value
Age, years, mean (SD)	74.4 (±12.0)	76.1 (±12.6)	0.002*
Gender, n (%)			
Male	358 (59.6)	273 (52.9)	0.03*
Medical history, n (%)			
HTN	404 (67.2)	336 (65.1)	0.46
CHF	154 (25.6)	96 (18.6)	0.005*
Diabetes	139 (23.1)	97 (18.8)	0.08
Cerebrovascular disease	108 (18.0)	100 (19.4)	0.55
MI	108 (18.0)	79 (15.3)	0.24
Embolic events (DVT, pulmonary embolism etc.)	55 (9.2)	28 (5.4)	0.02*
Peripheral vascular disease	41 (6.8)	29 (5.6)	0.41
$CHADS_{2,}$ median (IQR)	2.0 (1-3)	2.0 (1-3)	0.96
Low (score 0)	63 (10.5)	67 (13.0)	0.06
Intermediate (score 1)	165 (27.5)	112 (21.7)	
High (score 2-6)	373 (62.1)	337 (65.3)	
CHA_2DS_2-VASC, median (IQR)	4 (2-5)	4 (2-5)	0.99
Low (score 0)	16 (2.7)	20 (3.9)	0.20
Intermediate (score 1)	53 (8.8)	54 (10.5)	
High (score 2-6)	532 (88.5)	442 (85.7)	
HAS-BLED, median (IQR)	2.0 (1-2)	2.0 (1-2)	0.21
Low (score 0)	45 (7.5)	38 (7.4)	0.60
Intermediate (1-2)	451 (75.0)	376 (72.9)	
High (≥3)	105 (17.5)	102 (19.8)	
CCI, median (IQR)	5.0 (4-7)	5.0 (4-6)	0.43
0	50 (8.3)	46 (8.9)	0.43
1-2	26 (4.3)	16 (3.1)	
3-4	134 (22.3)	132 (25.6)	
≥5	391 (65.1)	322 (62.4)	
AF duration, n (%)			
New onset	153 (26.2)	159 (31.5)	0.06
Old	430 (73.8)	346 (68.5)	

AF, atrial fibrillation; CCI, Charlson comorbidity index; CHF, congestive heart failure; DVT, deep vein thrombosis; HTN, hypertension; MI, myocardial infarction; IQR, interquartile range; SD, standard deviation.
*= $P<0.05$

3.3.2 Anticoagulant prescribing pattern among patients with NVAF at discharge

Among those anticoagulated in the total population (n=601/1117), the majority of the patients were taking warfarin (61.7%) followed by a combination of warfarin and antiplatelet (24.8%), dabigatran (2.5%), and dabigatran plus antiplatelet (0.7%). The proportion of eligible patients treated with anticoagulant alone, combination therapy, antiplatelet alone or no treatment at

various levels of stroke risk ($CHADS_2$) is shown in Figure 3.1. Of patients with a high-risk of stroke ($CHADS_2 \geq 2$), 52.5% (n=373/710) were prescribed anticoagulant therapy. Two hundred and sixty-four (37.2%) of these patients were prescribed antiplatelet therapy and seventy-three (10.3%) patients were not on any antithrombotic treatment. Physician's decision was the most commonly documented reason for not providing anticoagulant treatment at discharge to the eligible patients at high-risk of stroke (n=44; 6.2%), followed by 'patient refusal' (n=22; 3.1%), 'falls risk' (n=22; 3.1%), 'non-adherence' (n=5; 0.7%), and 'adverse drug reaction' (n=3; 0.4%). Among those with a high-risk of stroke ($CHADS_2 \geq 2$), only 3.2% (n=23) had a HAS-BLED score that exceeded their $CHADS_2$ score. Among those at lower risk of stroke ($CHADS_2=0$) and receiving anticoagulant therapy, only 6.2% (n=8/130) had a history of embolic diseases other than AF where anticoagulation may have been indicated.

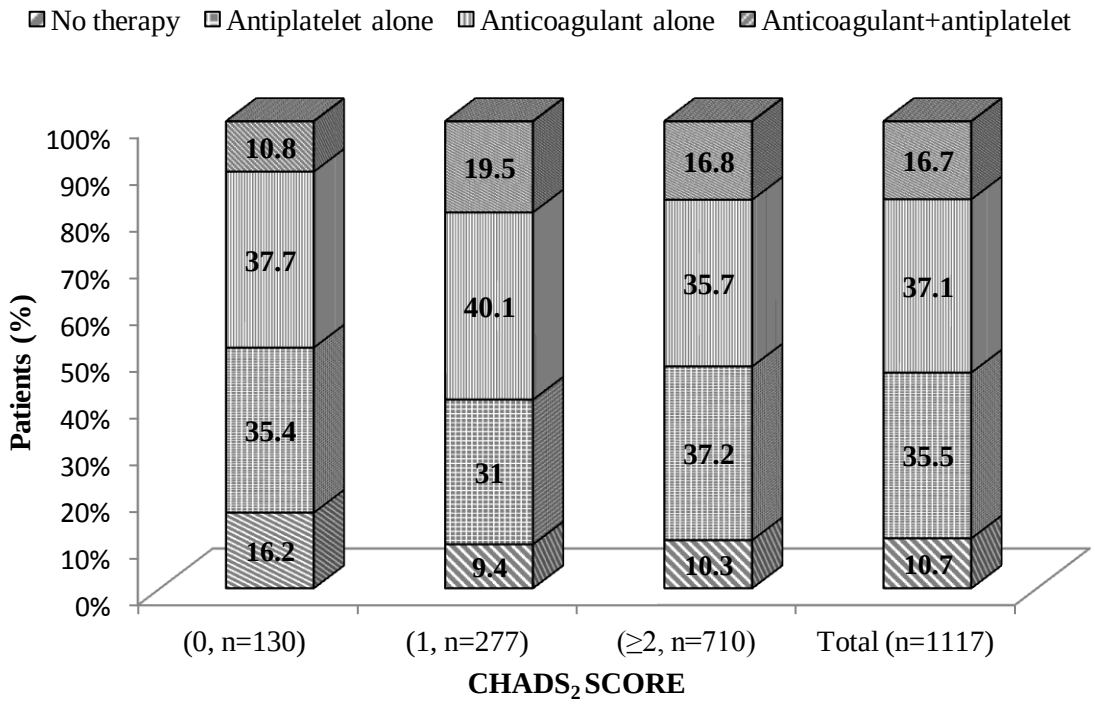


Figure 3.1 Antithrombotic prescribing pattern among patients with NVAF based on $CHADS_2$ score

When we compared the rate of anticoagulant prescribing among high-risk patients to that 15 years ago in Tasmania, there appeared to be an increase in the rate (52.5% vs. 42.1%) of prescribing. Nearly 10% of the high-risk patients did not receive any therapy (18.2% 15 years ago) and 48.5% of low-risk patients were anticoagulated (14.2% in the earlier cohort).

3.3.3 Factors associated with anticoagulant prescribing at discharge

We considered patients with NVAF and without CIs as eligible for anticoagulant therapy. Multivariate logistic regression included seven variables: age, gender, stratified $CHADS_2$ (with $CHADS_2$=0 as reference category), history of diabetes, CHF, embolic disease, and pre-admission AF. Younger age (odds ratio [OR] 0.99, 95% CI 0.97-1.0; P=0.04), $CHADS_2$=1 (OR 1.68, 95% CI 1.07-2.63; P=0.02), CHF (OR 1.56, 95% CI 1.12-2.15; P=0.008) and embolic disease history

(OR 1.77, 95% CI 1.09-2.86; P=0.02) were independently associated with anticoagulant prescribing (Table 3.2).

Table 3.2 Univariate and multivariate logistic regression of risk factors for anticoagulant prescribing among eligible patients with NVAF

Odds of anticoagulant prescribing	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age	0.99 (0.98-1.0)	0.01*	0.99 (0.97-1.0)	0.04*
Sex				
Female	0.76 (0.60-0.97)	0.03*	0.84 (0.65-1.08)	0.18
CHADS2				
0 (ref)				
1	1.57 (1.03-2.38)	0.04*	1.68 (1.07-2.63)	0.02*
2	1.08 (0.72-1.60)	0.72	1.13 (0.70-1.83)	0.62
≥3	1.30 (0.87-1.95)	0.20	1.19 (0.69-2.03)	0.53
Comorbidities				
CHF	1.51 (1.13-2.01)	0.005*	1.56 (1.12-2.15)	0.008*
HTN	1.10 (0.86-1.41)	0.46		
Diabetes	1.30 (0.97-1.74)	0.08	1.25 (0.90-.1.75)	0.19
CVD	0.91 (0.67-1.23)	0.55		
Embolic history	1.76 (1.10-2.81)	0.02*	1.77 (1.09-2.86)	0.02*
AF onset				
New (ref)				
Old	1.29 (0.99-1.68)	0.06	1.18 (0.90-1.55)	0.25

AF, atrial fibrillation; CHF, congestive heart failure; CVD, cerebrovascular disease; CI; confidence interval; HTN, hypertension; NVAF, non-valvular atrial fibrillation; OR, odds ratio.

3.4 Discussion

Nearly two-thirds of our patient cohort was at high-risk of stroke. We observed underutilisation of anticoagulant therapy among these eligible high-risk patients. Our data suggest that, despite an improvement in prescribing of anticoagulant therapy over the past 15 years, there remains significant potential for reduction in stroke outcomes with improved use of antithrombotic prophylaxis in the Tasmanian AF population. Despite guideline recommendations, we did not observe $CHADS_2 \geq 2$ as a significant predictor of anticoagulant prescribing in our population.

Underuse of anticoagulant therapy among high-risk groups has been frequently reported.(103, 116, 194, 212) In our study, only half of the patients in the high-risk group were receiving anticoagulant treatment. There was an apparent preference for lone antiplatelet therapy, with nearly one-third of our high-risk population receiving this therapy.

The observed improvements in anticoagulant prescribing among high-risk AF patients in Tasmania most likely reflect increased focus on the importance of effective thromboprophylaxis as recommended in international guidelines, as well as results of previous local intervention studies.(7, 16, 208) In contrast, we observed that the proportion of low-risk patients receiving anticoagulant therapy was higher now than 15 years ago. This appears to reflect current trends, however, as use of anticoagulant therapy in this group was similar to the GARFIELD study.(103) Embolic diseases other than AF may have resulted in some patients at low risk of stroke receiving anticoagulant therapy in our study, as embolic history was an independent predictor of anticoagulation. Alternatively, physicians' clinical judgement of stroke risk may have compelled them to consider factors beyond those included in $CHADS_2$.(103)

Several observational studies have reported on factors influencing anticoagulant prescribing patterns.(213, 214) Although prescribing guidelines for patients with intermediate risk of stroke were unclear at the time of our study (antiplatelet or anticoagulant therapy was indicated), (7, 16) the association between intermediate stroke risk ($CHADS_2$ score of 1) and anticoagulation use, instead of high risk ($CHADS_2 \geq 2$), relative to a $CHADS_2$ score of 0 was surprising. Existing guidelines clearly recommended prescription of anticoagulant therapy among those with a $CHADS_2 \geq 2$,(7, 16) but in alignment with previous studies conducted in

China and Turkey (210, 211) we did not find $CHADS_2 \geq 2$ as a predictor of anticoagulant prescribing. We hypothesised that this finding may have been due to high bleeding risk among these patients (given the overlap between stroke and bleeding risk factors), but only 3.2% of patients within this group had a HAS-BLED score higher than their $CHADS_2$ score. We identified physicians' decision to be the most common reason for not prescribing anticoagulant treatment to high-risk patients without any CIs. Bleeding is one of the most feared complications of anticoagulant use among treating physicians;(205) this may have influenced physicians' prescribing decisions in our study. This apparent discrepancy may further highlight the previously documented issue of *quantifiable* versus *perceived* bleeding risk by clinicians, and this issue requires further study if we are to make meaningful improvements in underprescribing of anticoagulants in patients at high risk of stroke.

A history of CHF and embolic disease, and younger age were the only other independent predictors of anticoagulant prescribing in our population. CHF has been previously associated with a higher rate of oral anticoagulation use,(212) and previous TE is now clearly acknowledged as a risk factor for stroke through its inclusion in the CHA_2DS_2-VASc scoring system.(20) We observed older age as a negative predictor for anticoagulant prescribing. Studies have identified underuse of anticoagulant therapy among elderly people due to the fear of bleeding.(197, 215) In contrast, benefits of anticoagulant therapy have been proven in clinical trials conducted among elderly patients (204, 216) and hence their use should not be discounted among elderly high-risk groups.

3.5 Conclusions

Our results suggest that there has been some improvement in the use of anticoagulant therapy among high-risk patients with AF over the past 15 years. Despite this improvement, further gains are required, and improved adherence to stroke risk stratification schemes for antithrombotic prophylaxis in AF could potentially reduce stroke outcomes in our population.

Chapter 4

Chapter 4: Hospital Readmission for Bleeding or Thromboembolic Complications in Patients with Newly Diagnosed Atrial Fibrillation

4 Abstract

This study was designed to examine the rates of, and factors associated with, hospital readmissions due to bleeding or thromboembolism (TE) among patients newly diagnosed with AF. We recruited patients admitted to the Royal Hobart Hospital in Tasmania, Australia, with newly diagnosed AF between January 2011 and June 2012. Patients were then followed for at least 18 months from the discharge date of their index admission to identify subsequent admissions for major bleeding or TE. In total, 257 patients (≥18 years) were included. The rates per 100 person-years (PY) of bleeding and TE-related readmissions within 3 months were 4.8 (95% CI 2.2-7.5) and 8.1 (95% CI 4.8-11.4), respectively. The rates per 100 PY of bleeding and TE-related readmissions during a mean of 2.1 years' follow-up were 1.5 (95% CI 0.02-3.0) and 3.7 (95% CI 1.4-6), respectively. Patients with peripheral vascular disease (PVD) (odds ratio (OR) 7.7, 95% CI 1.2-49.3) and renal impairment (OR 14.7, 95% CI 2.2-99.5) were more likely to be readmitted for bleeding, while those with a history of myocardial infarction (MI) (OR 6.3, 95% CI 2.2-18.1) were more likely to be readmitted for TE during longer-term follow-up. The rates of bleeding or TE-related readmissions were high in the initial 3 months in this cohort. Patients with PVD and renal impairment were at higher risk of bleeding and those with history of MI were at higher risk of TE during longer-term follow-up. These patients should be a focus of interventions to reduce adverse events in AF.

4.1 Introduction

Atrial fibrillation (AF) is a major risk factor for stroke and thromboembolism (TE).(12) The risk increases further with a previous history of stroke or transient ischaemic attacks (TIA), and a number of other known risk factors.(13) Stroke prevention is therefore a vital component of AF management. All contemporary guidelines recommend stroke prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke.(7, 16) Importantly, as bleeding is the most feared complication of oral anticoagulant therapy (OAC) therapy, the choice of appropriate antithrombotic therapy for stroke prevention in patients with AF requires a balance between the risk of stroke and risk of bleeding.(7)

AF is known to be associated with a high rate of hospital readmission (217, 218) due to complications including bleeding and TE. One population-based study of warfarin-treated patients with AF in the United Kingdom reported the incidence of vascular events (myocardial infarction (MI), stroke or systemic arterial peripheral embolism) and bleeding-related hospitalisations to be 3.8 per 100 patient-years and 3.3 per 100 patient-years, respectively.(219) It is established that the rates of bleeding or TE-related adverse effects are highest in the first 3 months of anticoagulant treatment in patients with AF.(220, 221) It has been suggested that the excess bleeding and mortality risk during initiation of anticoagulant therapy is a result of the unmasking of occult lesions or problems with International Normalised Ratio (INR) monitoring and warfarin dose adjustments during this period.(220) Monitoring the outcomes of patients with AF after initiation of antithrombotic treatment thus could play a significant role in minimising fatal bleeding and TE-related events in these patients. Although there are data regarding antithrombotic treatment patterns among patients with AF in Australia (117, 203), the data are

limited with respect to the rates of, and risk factors associated with, bleeding or TE-related hospitalisation. Our study examined the rates of readmissions due to bleeding or TE during short-term and longer-term follow-up periods among patients with newly diagnosed AF at the major hospital in Tasmania, Australia. We also identified the risk factors for readmission due to bleeding or TE during longer-term follow-up period.

4.2 Methods

4.2.1 Study design

We reviewed the records of patients aged ≥ 18 years with a primary or additional diagnosis of AF at discharge from the Royal Hobart Hospital (RHH), between 1st January 2011 and 30th June 2012. The RHH is a 500-bed teaching hospital for the southern region of Tasmania (population ≈ 260,000).(199) For this study, patients with either newly diagnosed non-valvular or valvular AF (Australian Refined Diagnosis-Related Group (AR-DRG) code I48: atrial fibrillation or flutter) during their index admission were included. Patients were excluded if they had only one episode of AF that reverted spontaneously or upon cardioversion without any documented recurrences, as stroke prophylaxis is not warranted in these groups of patients. Data collected at baseline included patient demographics, medication on admission and discharge, previous medical history, relevant laboratory data, and discharge diagnoses.

The $CHADS_2$ and CHA_2DS_2-VASc scores were used to estimate stroke risk. The $CHADS_2$ score was derived by allocating one point each for congestive heart failure (CHF), hypertension (HTN), age ≥75 years or diabetes, and two points for previous stroke or TIA.(17) The CHA_2DS_2-VASc score was calculated by assigning one point each to CHF, HTN, diabetes,

vascular disease (prior MI, peripheral artery disease or aortic plaque), age 65-74 years or female gender, and two points for age ≥75 years and previous stroke or TIA or TE.(20) The HAS-BLED score, used to estimate bleeding risk, was derived by allocating one point each for HTN, abnormal renal function (dialysis, transplant, serum Cr>200µmol/L), abnormal liver function (cirrhosis or bilirubin>2×normal or AST/ALT/AP>3×normal), previous stroke, bleeding pre-disposition, age >65 years, labile INRs (defined as documented unstable/high INRs), the use of drugs predisposing patients to bleeding (e.g. non-steroidal anti-inflammatory drugs [NSAIDs]) and alcohol use (>8 drinks per week).(33) CHA_2DS_2-VASc and HAS-BLED were included in our analysis to assist in our interpretation of results and provide a modern context, although it is acknowledged that they were not available to clinicians during the study period. The Charlson Comorbidity Index (CCI) was used as a measure of comorbidity.(200)

For the purposes of this analysis, patients were grouped according to the antithrombotic therapy (anticoagulant and/or antiplatelet medications) they received at discharge from their index admission. The 'antiplatelet' group consisted of patients receiving aspirin, clopidogrel, prasugrel, dipyridamole or ticagrelor, either alone or in combination with each other but not in combination with an anticoagulant. The 'lone anticoagulant' group consisted of patients receiving one of warfarin, dabigatran, heparin, fondaparinux or enoxaparin at discharge. Patients taking a combination of an anticoagulant medication with an antiplatelet agent constituted the 'combination therapy' group. Our definition of 'anticoagulant therapy' for this study comprised anticoagulant therapy, with or without concomitant antiplatelet therapy. We considered a patient's index admission as their first admission within our data collection period with a diagnosis of AF that met the study's inclusion criteria. During short-term follow-up, patients

were followed for 3 months from time of hospital discharge after their index admission with newly diagnosed AF or until the occurrence of a primary outcome or death, whichever came first. Similarly, for longer-term follow-up, patients were followed for at least 18 months from time of hospital discharge after their index admission with newly diagnosed AF, or until the occurrence of a primary outcome, death or December 31, 2013, whichever occurred first. Our primary outcomes were readmissions due to: 1) major bleeding, including haemorrhagic stroke requiring hospitalisation, and 2) TE (ischaemic stroke and systemic embolism, MI and TIA). Systemic embolism (SE) included an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts). Major bleeding was defined as fatal or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20g/L (1.24 mmol/L) or more, or leading to transfusion of at least two units of packed red blood cells.(222)

We calculated the incidence rate (number of events per 100 person-years [PY]) of each event for each treatment group and overall by dividing the numbers of major bleeding or TE events by the PY of exposure.

4.2.2 Statistical analysis

Data were analysed using SPSS version 21 (Prentice Hall, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. The rates of major bleeding and TE among different antithrombotic therapies were compared using the Kaplan-Meier method and log-rank test. In order to identify

the predictors of hospitalisation due to major bleeding or TE, we calculated odds ratio (ORs) and 95% confidence intervals (CIs) using binary logistic regression analysis and considered variables with a P value ≤0.2 as candidates for multivariate analysis. A multivariate analysis was carried out using the 'Enter' method to determine the independent predictors for longer-term readmission due to major bleeding or TE. The *a priori* level of significance was <0.05 for all analyses.

Ethics approval for the project was obtained from the Tasmanian Health and Medical Human Research Ethics Committee.

4.3 Results

4.3.1 Baseline data

The medical records of 1245 patients were reviewed, of whom 777 were included and 468 were excluded (episode of AF that reverted spontaneously or upon cardioversion: 228, developed AF as a short-term complication: 179, no documented AF [coding error]: 61). Forty-seven (6.1%) index admissions were excluded due to death of the patient or unavailability of their records. Of those discharged alive, 35.2% (n=257) had newly diagnosed AF and were thus included in this analysis (Figure 4.1). The characteristics of the patients with newly diagnosed AF are shown in Table 4.1.

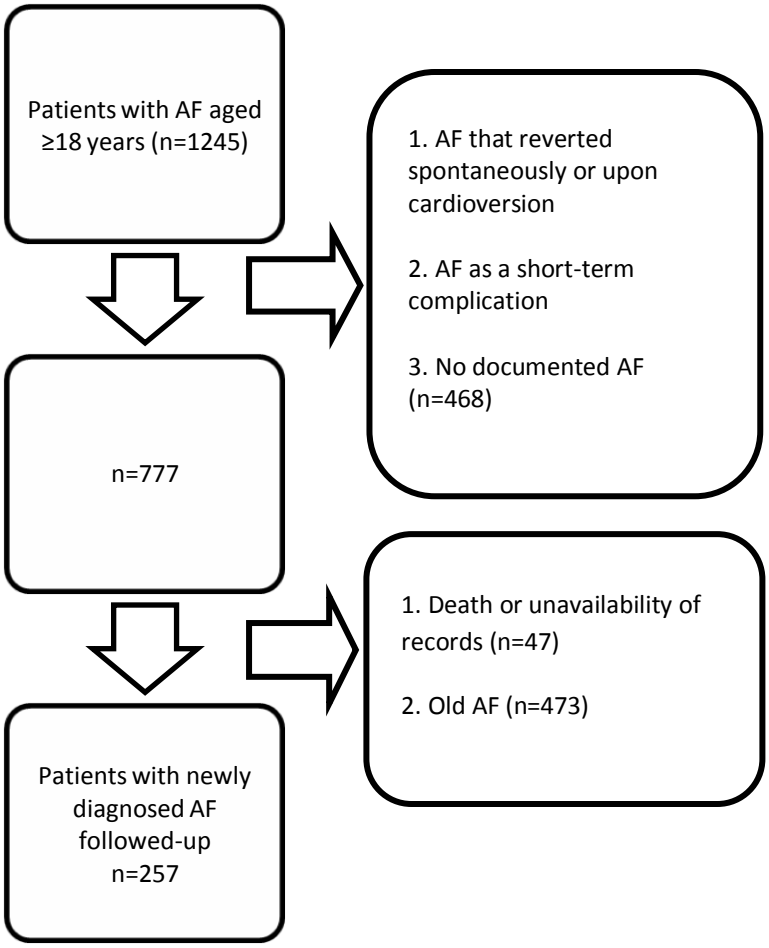


Figure 4.1. Study flowchart
Abbreviation: AF, atrial fibrillation

Table 4.1 Baseline characteristics of New AF patients enrolled in TAF study

Variables	All patients (n=257)
Age in years, Mean ± SD	74.4 ± 12.3
Men, n (%)	134 (52.1)
Medical history, n (%)	
Hypertension	177 (68.9)
Ischaemic heart disease	86 (33.5)
Chronic respiratory disease	55 (21.4)
Diabetes	45 (17.5)
Cerebrovascular disease	42 (16.3)
Myocardial infarction	35 (13.6)
Congestive heart failure	19 (7.4)
Peripheral vascular disease	12 (4.7)
Embolic events (DVT, Pulmonary embolism)	9 (3.5)
History of bleeding	6 (2.3)
Valvular heart disease, n (%)	26 (10.1)
CCI (classic), Mean ± SD	4.6 ± 2.3
$CHADS_{2,}$ Mean ± SD	1.8 ± 1.2
Low (score 0)	39 (15.2%)
Intermediate (score 1)	66 (25.7%)
High (score 2-6)	152 (59.1%)
CHA_2DS_2-VASc, Mean ± SD	3.3 ± 1.7
Low (score 0)	11 (4.3%)
Intermediate (score1)	31 (12.1%)
High (score 2-9)	215 (83.7%)
HAS-BLED, Mean ± SD	1.6 ± 0.9
Low (score 0)	27 (10.5%)
Intermediate (score 1-2)	192 (74.7%)
High (score ≥3)	38 (14.8%)
Antithrombotic therapy (on admission), n (%)	
Antiplatelet therapy	128 (49.8)
Anticoagulant therapy	10 (3.9)
AP/AC combination	7 (2.7)
No antithrombotic therapy	112 (43.6)
Reason for index admission, n (%)	
Related to AF	112 (43.6)
Bleeding	3 (1.2)
Thromboembolism	25 (9.7)
Other cardiovascular conditions	54 (21.0)
None of the above	63 (24.5)

AP/AC, antiplatelet and anticoagulant; AF, atrial fibrillation; CCI, Charlson comorbidity index; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke/transient ischaemic attack; CHA_2DS_2-VASC, congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke/transient ischaemic attack/systemic embolism, vascular disease, age 65-74 years, sex category; DVT, deep vein thrombosis; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or pre-disposition, labile international normalised ratio, Age >65 years, drugs/alcohol concomitantly; SD, standard deviation.

4.3.2 Incidence rates of major bleeding and TE

During the 3-month follow-up period, 3 bleeding and 5 TE events were identified; while during a mean of 2.1 years' follow-up, 8 bleeding and 19 TE events were recorded. A total of 61.95 PY for bleeding outcomes, and 61.88 PY for TE outcomes were identified for short-term follow-up and a total of 528.91 PY for bleeding outcomes, and 518.69 PY for TE outcomes were identified for longer-term follow-up. The incidence rates of readmission due to bleeding or TE during the two follow-up periods are shown in Table 4.2. Incidence rates of bleeding or TE events based on antithrombotic therapy during the two follow-up periods are shown in Table 4.3. We did not observe significant differences in bleeding or TE outcomes among different treatment categories.

Table 4.2 Event rates of major bleeding and thromboembolic events during short and longer-term follow-up periods

Events	3 months events	[a]Incidence rate per 100 person years; [b]% (95% CI)	18 months events	[a]Incidence rate per 100 person years; [b]% (95% CI)
Major bleeding	3	4.8 (2.2-7.5)	8	1.5 (0.02-3.0)
GIB	1	1.6 (0.1-3.2)	3	0.6 (-0.4-1.5)
ICH	-	-	1	0.2 (-0.3-0.7)
Others*	2	3.2 (1.1-5.4)	4	0.8 (0.3-1.8)
Thromboembolic	5	8.1 (4.8-11.4)	19	3.7 (1.4-6)
Ischaemic stroke/SE	3	4.9 (2.2-7.5)	11	2.1 (0.4-3.9)
MI	1	1.6 (0.1-3.2)	7	1.2 (-0.1-2.8)
TIA	1	1.6 (0.1-3.2)	1	0.2 (-0.3-0.7)

GIB, gastrointestinal bleeding; ICH, intracranial haemorrhage; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack
*Others: epistaxis, retroperitoneal bleeding.

[a]$\text{Incidence rate per } 100 \text{ person years} = \frac{\text{Number of readmissions for each event}}{\text{Person}-\text{years of exposure for each event}} \times 100$

[b]% (95% CI): Incidence rates presented with 95% confidence intervals.

Table 4.3 Major bleeding and thromboembolic readmission rates according to antithrombotic therapy on discharge

No. of major bleeding readmissions	NT (27)	AP (114)	AC (60)	Combination (56)	P value
3 months	0	1	0	2	0.27
Person-years of follow-up	6.4	27.8	14.6	13.2	
[a]Incidence rate/100 person-years, [b]% (95% CI)	0	3.6 (0.2-7.0)	0	15.2 (4.3-22.0)	
18 months	0	3	1	4	0.25
Person-years of follow-up	52.7	238.9	122.5	114.8	
[a]Incidence rate/100- person-years, [b]% (95% CI)	0	1.3 (-0.8-3.4)	0.8 (-1.5-3.1)	3.5 (-1.2-8.3)	
No. of thromboembolic readmissions					
3 months	1	1	1	2	0.58
Person-years of follow-up	6.3	27.8	14.6	13.3	
[a]Incidence rate/100- person-years, [b]% (95% CI)	7.0 (-2.6-16.6)	3.6 (0.2-7.0)	6.9 (0.5-13.3)	15.1 (5.7-24.5)	
18 months	4	8	3	4	0.26
Person-years of follow-up	48.4	232.4	122.3	115.5	
[a]Incidence rate/100- person-years, [b]% (95% CI)	8.3 (-2.1-18.7)	3.4 (0.1-6.7)	2.5 (-1.5-6.5)	3.5 (-1.3-8.3)	

NT, no therapy; AP, antiplatelet therapy; AC, anticoagulant therapy; Combination: (AP+AC)

[a]$\text{Incidence rate}/100\ \text{person} - \text{years} = \frac{\text{Number of readmissions within each group}}{\text{Person}-\text{years of exposure for each group}} \times 100$

[b]% (95% CI): Incidence rates presented with 95% confidence intervals.

4.3.3 Predictors of major bleeding and TE-related readmission

Multivariate logistic regression performed to identify predictors of longer-term readmission due to bleeding included three variables: CHF, peripheral vascular disease (PVD) and discharge estimated glomerular filtration rate <30 mL/min/1.73m^2 (eGFR <30). Notably, we did not any relationship between HAS-BLED score and bleeding-related readmission in our analysis (P=0.83). Longer-term readmission due to bleeding was independently associated with history of PVD (OR (odds ratio) 7.7, 95% CI 1.2-49.3; P=0.03) and an eGFR <30 (OR 14.7, 95% CI 2.2-99.5; P=0.006) (Table 4). All of the patients with the history of PVD and readmitted due to bleeding were taking combination therapy at the time of their readmission although antithrombotic therapy itself did not predict readmission. Similarly, multivariate regression carried to identify predictors of longer-term readmission due to TE included four variables: history of HTN, MI, diabetes and cerebrovascular disease. Prior history of MI was the only risk factor independently associated with an increased likelihood of longer-term readmission due to TE (OR 6.3, 95% CI 2.2-18.1; P <0.001) (Table 4.4).

Table 4.4 Multivariate analysis of association between potential predictors and readmission for longer-term major bleeding or thromboembolism

Major bleeding readmissions	**Comorbidities**	**[a]OR (95% CI)**	**P value**
	Peripheral vascular disease	7.7 (1.2-49.3)	0.03[b]
	Discharge eGFR		
	<30	14.7 (2.2-99.5)	0.006[b]
	30-60	2.8 (0.4-18.2)	0.28
	>60 (ref)		
Thromboembolic readmissions	**Comorbidities**	**[a]OR (95% CI)**	**P value**
	Myocardial infarction	6.3 (2.2-18.1)	<0.001[b]

eGFRr, estimated glomerular filtration rate in mL/min/1.73 m^2

[a]OR (95% CI): odds ratio presented with 95% confidence intervals.

[b]P < 0.05

4.4 Discussion

Our 3-month event rates per 100 PY for major bleeding and TE were higher than the rates at longer-term follow-up. The risk of bleeding in particular has been found to be highest early in the course of anticoagulant therapy.(223) Other real-world studies have also reported that the rates of bleeding or TE-related adverse events are higher in the first 3 months of anticoagulant treatment in patients with AF.(220, 221) Poor anticoagulation control after hospital initiation of warfarin has been well reported, (224) and we hypothesize that this may have contributed to our higher 3-month event rates. We were unable to demonstrate a difference in event rates between agents, however, potentially due to the low overall number of events; a larger study would be required to confirm this hypothesis.

In randomized controlled trials involving patients with AF, the incidence of major bleeding due to antithrombotic treatment was reported to range between 1 and 3% per person-year.(74, 81, 82, 225) When compared to data reported in the recent clinical trials comparing direct acting oral anticoagulants to warfarin, (66, 71, 74, 76) our longer-term rates per 100 PY of major bleeding (1.5 vs. 0.50-4.20/year) and stroke/SE (2.1 vs. 1.10-2.20/year) were comparable. In comparing our rates to a 'real-world' study, while the longer-term rate per 100 PY of stroke/SE event was comparable (2.1 vs. 2.97%), our rate per 100 PY of major bleeding event was lower than the rate previously reported (1.5 vs. 6.22%).(226)

Our study also examined the risk factors associated with major bleeding or TE-related readmissions during a longer-term follow-up period in patients with AF. We identified that history of MI was the only predictor for TE-related readmission. The risk of stroke and/or the

composite thromboembolism endpoint (stroke, TIA, or systemic embolism) has been found to increase independently in the presence of vascular disease in patients with AF, (34) which is also reflected in the recent inclusion of MI as a risk factor for stroke in CHA_2DS_2-VASc. Guidelines regarding combination therapy in patients with AF and unstable coronary artery disease currently vary, (16, 227) and our results suggest a need for a particular focus on optimal prescribing in this group of patients.

Factors such as older age, alcohol excess, anaemia, and heart failure have been found as independent predictors of bleeding.(228) We instead observed a history of PVD and severe renal impairment as significant predictors of major bleeding-related readmissions during our longer-term follow-up. It should be acknowledged, however, that the confidence intervals are relatively wide, reflecting our sample size and the incidence of outcome measures. Vascular disease, including PVD, has been recently introduced into the risk assessment for patients with AF due to its inclusion in the CHA_2DS_2-VASc score. A history of PVD has not previously been associated with an increased risk of bleeding events in patients with AF. While this finding is likely due to the use of combination anticoagulant/antiplatelet therapy in this group, a larger study is again needed to confirm such a result. In the meantime, our finding suggests that closer monitoring is necessary while treating patients with AF and a history of PVD. Rates of bleeding have been found to increase with reducing eGFR, regardless of sex, age, or anticoagulant therapy.(229) Our observation that patients with reduced eGFR were more likely to suffer from major bleeding-related readmissions suggests the fact that patients with AF and renal impairment should also be closely monitored for major bleeding-related outcomes. Trials of OAC therapy (including direct acting oral anticoagulants) are required among these patients to establish the balance of efficacy

vs. safety of anticoagulant therapy as the majority of AF trials have excluded patients with chronic kidney disease.(229)

4.5 Conclusions

The prevalence of major bleeding or TE-related readmissions was high in initial 3 months in this cohort. Patients with a history of PVD and renal impairment were at higher risk of major bleeding and those with MI were at higher risk of TE during longer-term follow-up. Our findings suggest that these risk factors should be considered as 'red flags' when managing patients with AF, and patients with these conditions should receive special attention when managing concomitant AF. In fact, these patient groups are a potential target for intervention in future AF studies so as to minimise the incidence of major bleeding or TE-related hospitalisations.

Chapter 5

Chapter 5: Antithrombotic usage patterns and outcomes among elderly patients diagnosed with atrial fibrillation in Tasmania

5 Abstract

Longer-term follow-up data for elderly patients diagnosed with atrial fibrillation (AF) is sparse in Australia. This study was designed to compare the patient characteristics, antithrombotic prescribing patterns, and rates of major bleeding and thromboembolic (TE) outcomes between older and younger patients diagnosed with AF. We recruited patients admitted to the Royal Hobart Hospital in Tasmania, Australia, with diagnosed AF between January 2011 and June 2012. These patients were then followed for at least 18 months from the discharge date of their index admission to identify subsequent admissions for major bleeding or TE. In total, 730 patients (≥18 years) were included, of whom 374 (51.2%) were aged ≥75. Among high-risk patients aged ≥75 years, only 51.8% received anticoagulant treatment (vs. 64.6% in the younger group; P=0.02). After a mean follow-up of 2.2 years, elderly patients were observed to be at higher risk of major bleeding (hazard ratio (HR) 3.2, 95% CI) 1.4-7.5, P=0.004) but the incidence of TE did not differ significantly (HR 1.5, 95% CI 0.9-2.7, P=0.15) between the groups. Elderly patients prescribed anticoagulant therapy were at significantly higher risk of major bleeding (HR 3.0, 95% CI 1.1-8.3, P=0.02) but at similar risk of TE (HR 0.9, 95% CI 0.4-1.8, P=0.69) compared to those on no anticoagulant therapy. In this study, anticoagulant therapy was underused among high-risk elderly patients with AF compared to their younger counterparts. Elderly patients had higher incidence of major bleeding but similar risk of TE compared to younger patients in this cohort.

5.1 Introduction

Atrial fibrillation (AF) is associated with increased risks of cardiovascular and cerebrovascular complications including myocardial infarction (MI) and cardio-embolic stroke.(230, 231) Advanced age has been shown to be one of the major risk factors for AF-associated stroke in patients with AF. A number of studies have shown that AF is more common in people over the age of 65 years than their younger counterparts. AF is present in 0.12-0.16% of those younger than 49 years, in 3.7-4.2% of those aged 60-70 years, and in 10-17% of those aged 80 years or older.(90, 232) In the Framingham Study, 23.5% of strokes in individuals aged 80 years or older were attributable to AF.(233) Recent guidelines from Europe, America and other countries throughout the world recommend oral anticoagulant (OAC) prophylaxis in patients with AF and at high risk of stroke, (CHA_2DS_2-VASc $\geq$2).(6, 7, 234) However, use of OAC in the elderly is challenging as both stroke and bleeding risk increase with age.

Although the benefits of antithrombotic therapy in the elderly are well established, the elderly are more vulnerable to adverse effects of antithrombotic drugs. It has been shown that treatment with warfarin under careful monitoring is associated with a 0.3-0.5% increased risk of major bleeding per year compared with controls.(235) These rates may be higher in routine clinical practice, taking into account that data are mainly derived from younger cohorts and well-controlled patients rather than those observed in real life. In particular, there is a tendency towards a 2 to 3-fold increase in bleeding and intracranial haemorrhages (ICH) among elderly patients.(235, 236) Surveys have consistently revealed patient age as a deterrent to the use of OAC in AF. Physicians are reluctant to prescribe anticoagulants in elderly patients due to high risk of falls and risk of traumatic ICH, poor compliance, difficulty in monitoring, cognitive

impairment and risk of interaction with multiple other drugs.(132, 133) These issues may provide explanations for the substantial underutilisation of vitamin K antagonists in the elderly population. OAC therapy continues to be underutilised in older adults despite compelling evidence of benefits in stroke reduction in this age group. Studies have shown that, 30-50% of older adult patients without contraindication to OAC are not receiving anticoagulant therapy.(237, 238) However, even if elderly individuals have characteristics that may place them at higher risk for bleeding, they also have characteristics that make them more likely to benefit. The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trial, a randomized comparison of warfarin versus aspirin in 973 patients with AF age ≥75 years, revealed that the yearly risk of the combined primary end point of stroke, ICH, or clinically significant embolism was 1.8% in patients who received warfarin and 3.8% in those who received aspirin (relative risk: 0.48, 95% CI: 0.28 to 0.80, P<0.003).(204) Accordingly, age alone should not be a contraindication to OAC use as elderly patients with AF may benefit most from anticoagulation. Hence, anticoagulation in elderly patients requires careful assessment of risk of stroke against an equally high risk of major bleeding. Studies regarding use and outcomes of OAC in the elderly patients from routine clinical settings are limited throughout the world. To date, longer-term follow-up data for elderly patients diagnosed with AF is sparse in Australia. In this study we sought to examine and compare the patient characteristics, antithrombotic prescribing patterns, and rates of major bleeding or TE outcomes during longer-term follow-up between older and younger patients diagnosed with AF in Tasmania.

5.2 Materials and Methods

5.2.1 Study design

We reviewed the records of patients aged ≥18 years with a primary or secondary diagnosis of AF at discharge from the Royal Hobart Hospital (RHH), between 1st January 2011 and 30th June 2012. The RHH is a 500-bed teaching hospital for the southern region of Tasmania (population ≈ 260,000).(199) Patients diagnosed with either non-valvular or valvular AF (Australian Refined Diagnosis-Related Group code I48: atrial fibrillation or flutter) during their index admission were included for this study. We divided patients into two age groups - a younger group aged <75 and an older group aged 75 or above. We excluded patients if they had only one episode of AF that reverted spontaneously or upon cardioversion without any documented recurrences, as stroke prophylaxis is not warranted in these groups of patients.

The $CHADS_2$ and CHA_2DS_2-VASc scores were used to estimate stroke risk. We derived the $CHADS_2$ score by allocating one point each for congestive heart failure (CHF), hypertension (HTN), age ≥75 years or diabetes, and two points for previous stroke or transient ischaemic attack (TIA).(17) The CHA_2DS_2-VASc score was calculated by assigning one point each to CHF, HTN, diabetes, vascular disease (prior MI, peripheral artery disease or aortic plaque), age 65-74 years or female gender, and two points for age ≥75 years and previous stroke or TIA or TE.(20) We derived the HAS-BLED score, used to estimate bleeding risk, by allocating one point each for HTN, abnormal renal function (dialysis, transplant, serum Cr>200µmol/L), abnormal liver function (cirrhosis or bilirubin>2×normal or AST/ALT/AP>3×normal), previous stroke, bleeding pre-disposition, age >65 years, labile INRs (defined as documented unstable/high INRs), the use of drugs predisposing patients to bleeding (e.g. non-steroidal anti-

inflammatory drugs [NSAIDs]) and alcohol use (>8 drinks per week).(33) CHA_2DS_2-VASc and HAS-BLED were included in our analysis to assist in our interpretation of results and provide a modern context, although it is acknowledged that they were not available to clinicians during the study period. The Charlson Comorbidity Index (CCI) was used as a measure of comorbidity.(200)

Patients receiving aspirin, clopidogrel, prasugrel, dipyridamole or ticagrelor, either alone or in combination with each other but not in combination with an anticoagulant comprised the 'antiplatelet' treatment group. Patients receiving one of warfarin, dabigatran, heparin, fondaparinux or enoxaparin at discharge constituted 'lone anticoagulant' group. Patients taking a combination of an anticoagulant medication with an antiplatelet agent constituted the 'combination therapy' group. Our definition of 'anticoagulant therapy' for this study comprised anticoagulant therapy, with or without concomitant antiplatelet therapy. Our definition of 'no anticoagulant therapy' consisted patients either on 'no therapy' or 'antiplatelet therapy'. We considered a patient's index admission as their first admission within our data collection period with a diagnosis of AF that met the study's inclusion criteria. Patients were followed for at least 18 months from time of hospital discharge after their index admission or until the occurrence of a primary outcome, death or December 31, 2013, whichever occurred first. Our primary outcomes were: 1) major bleeding, including haemorrhagic stroke requiring hospitalisation, and 2) TE (ischaemic stroke and systemic embolism (SE), MI and TIA). Systemic embolism included an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts). Major bleeding was defined as fatal or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or

intramuscular with compartment syndrome, and/or bleeding causing a fall in haemoglobin level of 20g/L (1.24 mmol/L) or more, or leading to transfusion of at least two units of packed red blood cells.(222)

We calculated the incidence rate (number of events per 100 person-years [PY]) by dividing the numbers of events by the PY of exposure.

5.2.2 Statistical analysis

Data were analysed using SPSS version 21 (Prentice Hall, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequencies and percentages. The rates of major bleeding and TE among different groups were compared using the Kaplan-Meier method and log-rank test. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) between the two groups using univariate Cox regression analysis. The *a priori* level of significance was < 0.05 for all analyses.

We obtained ethics approval for the project from the Tasmanian Health and Medical Human Research Ethics Committee.

5.3 Results

5.3.1 Clinical characteristics

The medical records of 1245 patients were reviewed, of whom 777 were included and 468 were excluded (episode of AF that reverted spontaneously or upon cardioversion: 228, developed AF as a short-term complication: 179, no documented AF [coding error]: 61). Forty-seven (6.1%)

index admissions were excluded due to death of the patient or unavailability of their records. Thus for this analysis we included 730 patients. Comparisons of the characteristics of the patients aged <75 and ≥75 years are shown in Table 5.1. It was observed that the elderly patients were significantly more likely to have cardiovascular and renal comorbidities and were at higher risk of bleeding and TE as per their risk assessment scores.

Table 5.1: Baseline characteristics of patients according to age

Variable	≥75 (n=374)	<75 (n=356)	P value
Age, years, mean (SD)	83.5 (±12.0)	65.2 (±12.6)	<0.001*
Gender, n (%)			
Male	167 (44.7)	250 (70.2)	<0.001*
Medical history, n (%)			
HTN	262 (70.1)	212 (59.6)	0.003*
CHF	71 (67.2)	48 (13.5)	0.005*
Diabetes	73 (19.5)	78 (21.9)	0.43
Cerebrovascular disease	77 (20.6)	53 (14.9)	0.04*
MI	61 (16.3)	37 (10.4)	0.02*
Embolic events (DVT, pulmonary embolism etc.)	22 (5.9)	18 (5.1)	0.62
Peripheral vascular disease	16 (4.3)	18 (5.1)	0.62
Bleeding history	20 (5.3)	3 (0.8%)	<0.001*
Renal disease	25 (6.7)	11 (3.1)	0.03*
$CHADS_{2,}$ mean (±SD)	2.5 (±1.1)	1.3 (±1.1)	<0.001*
Low (score 0)	0 (0)	103 (28.9)	<0.001*
Intermediate (score 1)	67 (17.9)	126 (35.4)	
High (score 2-6)	307 (82.1)	127 (35.7)	
CHA_2DS_2-VASC, mean (±SD)	4.3 (±1.3)	2.4 (±1.5)	<0.001*
Low (score 0)	0 (0)	27 (7.6)	<0.001*
Intermediate (score 1)	0 (0)	85 (23.9)	
High (score 2-9)	374 (100%)	244 (68.5)	
HAS-BLED, mean (±SD)	2.0 (±0.8)	1.3 (±0.9)	<0.001*
Low (score 0)	1 (0.3)	63 (17.7)	<0.001*
Intermediate (score 1-2)	280 (74.9)	257 (72.2)	
High (≥3)	93 (24.9)	36 (10.1)	
CCI, mean (±SD)	5.8 (±1.8)	3.9 (±2.5)	<0.001*
AF duration, n (%)			
New onset	133 (35.6)	124 (34.8)	0.84
Old	241 (64.4)	232 (65.2)	
Discharge eGFR, n (%)			<0.001*
<30	39 (10.4)	29 (8.1)	
30-60	138 (36.9)	64 (18.0)	
>60	197 (52.7)	263 (73.9)	
Discharge antithrombotic therapy			
No therapy	45 (12.0)	30 (8.4)	0.11

Antiplatelet	138 (36.9)	115 (32.3)	0.19
Anticoagulant	191 (51.1)	211 (59.3)	0.03*

AF, atrial fibrillation; CCI, Charlson comorbidity index; CHF, congestive heart failure; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); HTN, hypertension; MI, myocardial infarction; SD, standard deviation. *= P<0.05

5.3.2 Anticoagulant prescribing pattern at discharge

We observed that elderly patients were significantly less likely to receive anticoagulant therapy (51.1% vs. 59.3%; P=0.03) compared to the younger group of patients during index admission discharge. There was also a significant difference in the rate of prescribing of anticoagulant therapy between the elderly and younger cohorts with a high risk of stroke ($CHADS_2 \geq 2$) - 51.8% vs. 64.6% (P=0.02). In addition, 12.1% of patients aged ≥75 years with a $CHADS_2$ score ≥2 were not receiving any antithrombotic treatment (vs. 3.9% younger group; P=0.009) (Figure 5.1). Elderly patients had significantly higher risk (HAS-BLED ≥3) of bleeding than the younger group (24.9% vs. 10.1%; P<0.001)). The mean HAS-BLED score of high-risk elderly patients was observed to be significantly higher than the younger group (2.1 vs. 1.8; P=0.002).

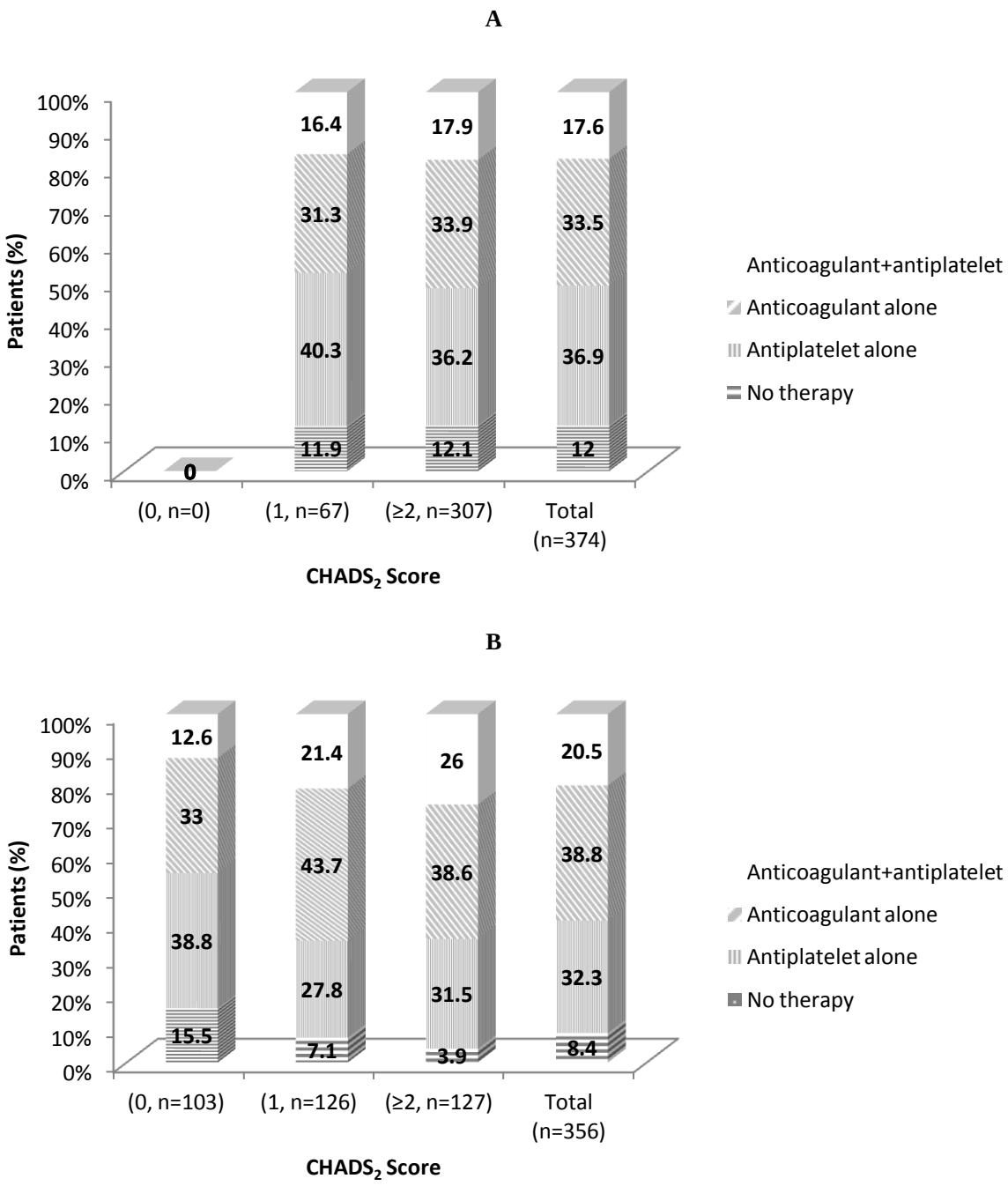


Figure 5.1: Antithrombotic prescribing pattern based on $CHADS_2$ scores at discharge (A) ≥75 (B) <75 years

5.3.3 Incidence rates of bleeding and TE

During a mean of 2.2 years follow-up in the entire cohort (a total of 1600.8 PY), 29 major bleeding and 51 TE events were recorded. The annual incidences of major bleeding were 0.8%

and 3.1% per 100 PY with age <75 and ≥75 years, respectively. Similarly, the annual incidences of TE were 2.6% and 4.1% per 100 PY with age <75 and ≥75 years, respectively. The incidence rates of events during the follow-up for the two groups are shown in Table 5.2. Kaplan-Meier curves for the incidence of major bleeding and TE among each group are shown in Figure 5.2. Elderly patients had a higher risk of major bleeding (HR (Hazard ratio) 3.2, 95% CI 1.4-7.5, P=0.004) compared to the younger patients. We did not observe a significant difference in TE outcomes between the groups (HR 1.5, 95% CI 0.9-2.7, P=0.15).

Elderly patients on anticoagulant therapy were at greater risk of major bleeding than those who were not (HR 3.0, 95% CI 1.1-8.3, P=0.02). There was no difference in the incidence rate of ICH between those treated and not treated with anticoagulant therapy (1.2 per 100 PY vs. 0.4 per 100 PY; P=0.13). We however observed similar risk of TE (HR 0.9, 95% CI 0.4-1.8, P=0.69) between the elderly patients who were anticoagulated and those who were not. When we assessed the differences in baseline characteristics in elderly patients who were and were not prescribed anticoagulants (Table 5.3), more patients receiving anticoagulant therapy had CHF (24.5% vs. 13.2%; P=0.005) and a history of embolic disease (8.9% vs. 2.7%; P=0.01), while those not receiving anticoagulant therapy had a frequent history of bleeding (8.2% vs. 2.6%; P=0.02). We did not observe any differences in the mean $CHADS_2$ (2.6 vs.2.4; P=0.16) or HAS-BLED (1.9 vs. 2.1; P=0.11) scores between patients prescribed and not prescribed anticoagulant therapy. Incidence rates of events in the elderly patients based on anticoagulant therapy during the follow-up are shown in Table 5.4. The associations between anticoagulant prescribing and the outcomes among elderly patients are shown in Figure 5.3.

Table 5.2: Event rates (/100 person-years) of major bleeding and TE events (entire cohort based on age group)

Events	<75 Total events (incidence rates)	≥75 Total events (incidence rates)	<75 vs. ≥75 HR (95% CI)[a]	P value
Major bleeding	7 (0.8)	22 (3.1)	3.2 (1.4-7.5)	0.004
TE	22 (2.6)	29 (4.1)	1.5 (0.9-2.7)	0.15
Ischaemic stroke/SE	13 (1.5)	15 (2.1)	1.4 (0.6-3.1)	0.39
MI				
TIA	4 (0.5)	12 (1.7)	2.8 (0.9-8.9)	0.06
	5 (0.6)	2 (0.3)	0.5 (0.1-2.8)	0.43

MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack; TE: thromboembolism.
*others: epistaxis, retroperitoneal bleeding.
[a] Hazard ratio presented with 95% confidence intervals.

$$\text{Incidence rate} = \frac{\text{Number of readmissions for each event within follow up period}}{\text{Person} - \text{years of exposure for each event}} \times 100$$

Person-years follow-up for bleed (<75)=868.97, TE=849.30
Person- years follow-up for bleed (≥75)=706.58, TE=702.78

Table 5.3: Baseline characteristics of elderly patients prescribed and not prescribed anticoagulants (n=374)

Variable	(-) anticoagulant (n=182)	(+) anticoagulant (n=192)	P value
Age, years, mean (SD)	84.0 (±5.9)	82.9 (±4.9)	0.14
Medical history, n (%)			
HTN	126 (69.2)	136 (70.8)	0.74
CHF	24 (13.2)	47 (24.5)	0.005*
Diabetes	29 (15.9)	44 (22.9)	0.09
Cerebrovascular disease	39 (21.4)	38 (19.8)	0.70
MI	31 (17)	30 (15.6)	0.71
Embolic events (DVT, pulmonary embolism etc.)	5 (2.7)	17 (8.9)	0.01*
Peripheral vascular disease	7 (3.8)	9 (4.7)	0.69
Bleeding history	15 (8.2)	5 (2.6)	0.02*
Renal disease	12 (6.6)	13 (6.8)	0.95
$CHADS_2$, mean (±SD)	2.4 (±1.1)	2.6 (±1.2)	0.16
CHA_2DS_2-VASC, mean (±SD)	4.2 (±1.3)	4.4 (±1.3)	0.10
HAS-BLED, mean (±SD)	2.1 (±0.8)	1.9 (±0.8)	0.12
CCI, mean (±SD)	5.7 (±1.8)	5.8 (±1.9)	0.65
Discharge antithrombotic therapy			<0.001*
No therapy	47 (25.8)	0 (0)	
Antiplatelet	135 (74.2)	0 (0)	
Combination	0 (0)	62 (32.2)	
Anticoagulant	0 (0)	130 (67.7)	

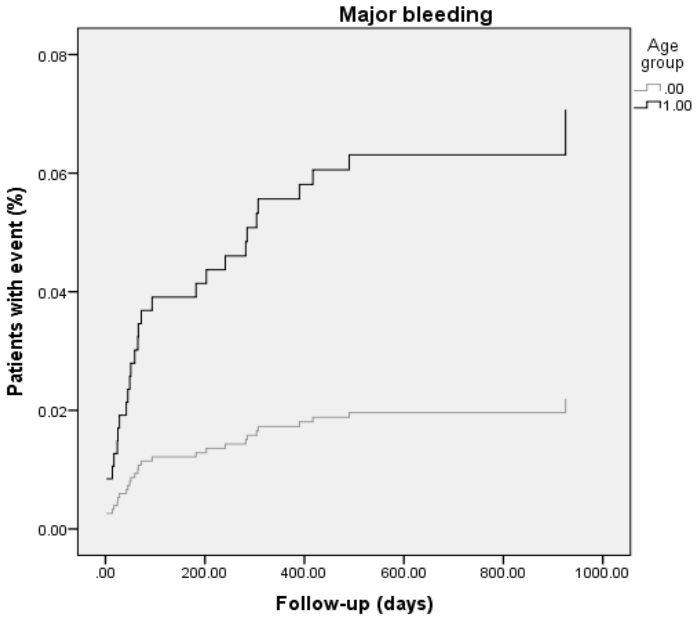
AF, atrial fibrillation; CCI, Charlson comorbidity index; CHF, congestive heart failure; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); HTN, hypertension; MI, myocardial infarction; SD, standard deviation.
*=P<0.05

Table 5.4: Major bleeding and TE rates (/100 person-years) according to anticoagulant therapy on discharge (elderly cohort: 374)

Events	(-) anticoagulant (182)	(+) anticoagulant (192)	HR (95% CI)[a]	P value
Major bleeding	5 (0.9)	17 (2.9)	3.0 (1.1-8.3)	0.02
TE	15 (4.7)	14 (3.7)	0.9 (0.4-1.8)	0.69
Ischaemic stroke/SE	7 (2.1)	8 (2.1)	1 (0.4-2.8)	1.0
MI	7 (2.1)	5 (1.3)	0.7 (0.2-2.3)	0.57
TIA	1 (0.3)	1 (0.3)	0.8 (0.1-13.1)	0.89

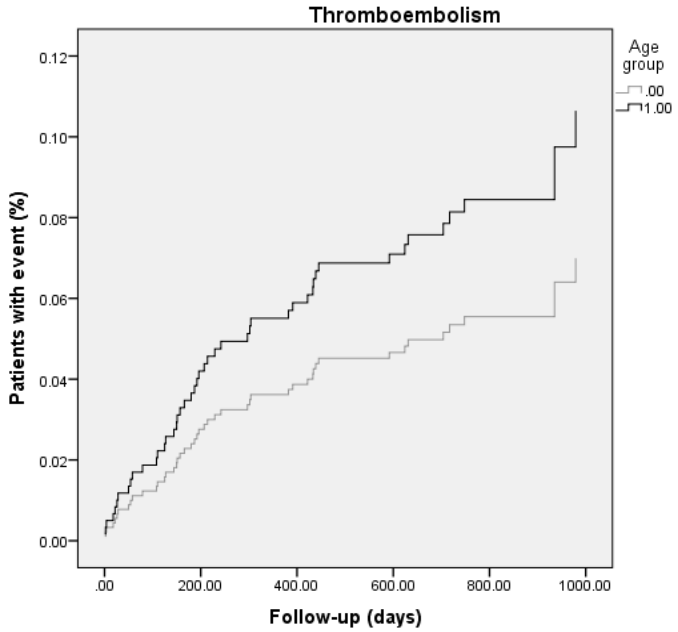
MI: myocardial infarction; SE: systemic embolism; TIA: transient ischaemic attack; TE: thromboembolism.
*others: epistaxis, retroperitoneal bleeding.
[a] Hazard ratio presented with 95% confidence intervals.
Person-years follow-up (- anticoagulant): bleed=559.92, TE=322.03
Person- years follow-up (+ anticoagulant): bleed=580.09, TE=380.76

A



HR (CI)=3.2 (1.4-7.5), Log rank; P=0.004

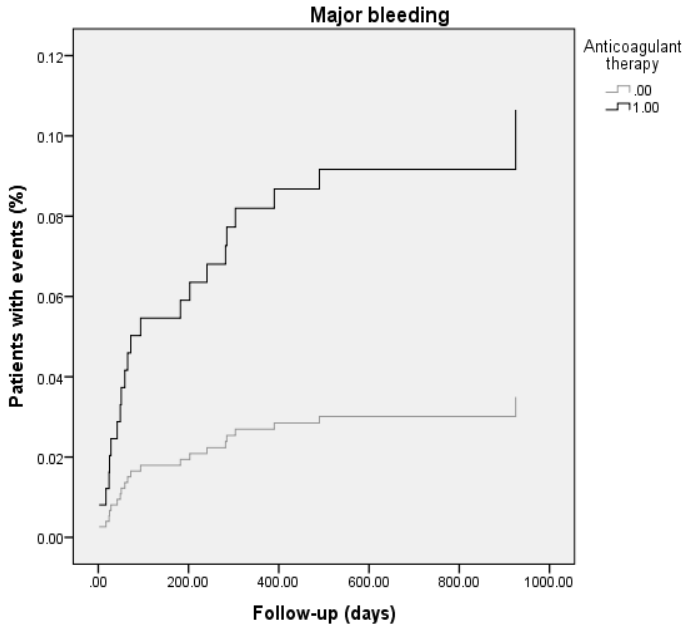
B



HR (CI)=1.5 (0.9-2.7), Log rank; P=0.15

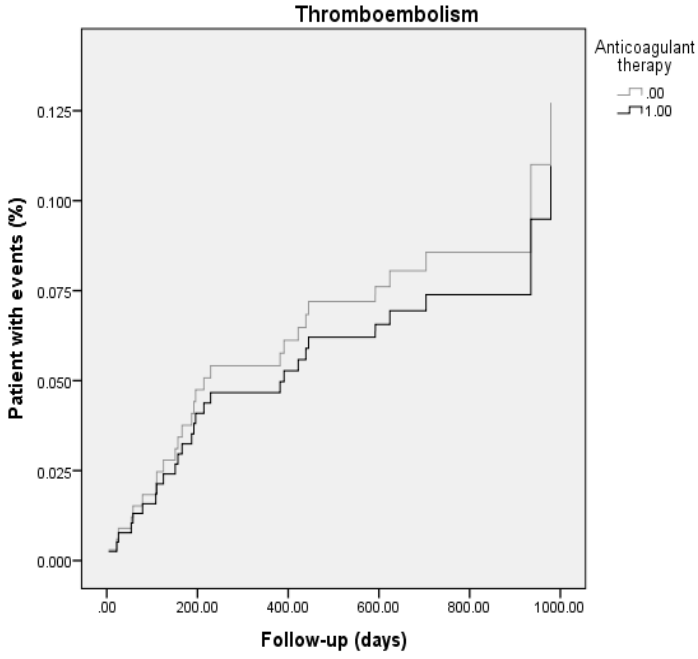
Figure 5.2: Cumulative hazard rates of (A) Major bleeding (B) TE, in patients <75 (=0) vs. ≥75 (=1) years

A



HR (CI)=3.0 (1.1-8.3), Log rank; P=0.02

B



HR (CI)=0.9 (0.4-1.8), Log rank; P=0.69

Figure 5.3: Cumulative hazard rates of (A) Major bleeding (B) TE, in patients ≥75 with (=1) or without (=0) anticoagulant therapy

5.4 Discussion

The Tasmanian Atrial Fibrillation (TAF) study is an observational study designed to comprehensively evaluate the management and outcomes of patients with AF. The dataset is the largest and most recent of its kind in Australia. In this paper, we compared the patient characteristics, antithrombotic prescribing patterns, and rates of major bleeding or TE outcomes between older and younger patients diagnosed with AF admitted to one of the major hospitals in Tasmania, Australia. We observed significant difference in the rate of prescribing of anticoagulant therapy between the elderly and younger cohorts. Being aged ≥75 years was however associated with a higher risk of major bleeding events and this was significantly associated with the use of anticoagulant therapy in this group of patients.

Despite all the proven benefits, early discontinuation and underuse of anticoagulant therapy in real-world practice have often been reported due to reasons like history of anaemia, history of hospitalisation/emergency room visits, elderly age, comorbidities, risk of falls and previous bleeding.(103, 133, 203, 206) Studies have identified underuse of anticoagulant therapy among elderly people due to the fear of bleeding.(197, 215) In contrast, benefits of anticoagulant therapy have been proven in clinical trials conducted among elderly patients.(204, 216) and hence their use should not be discounted among elderly high-risk groups. Risk of stroke has been shown to increase without anticoagulation therapy in patients ≥75 years.(73) In our study, only half of the high-risk elderly patients were receiving anticoagulant therapy. The underuse of anticoagulant therapy is likely to have been influenced by the higher bleeding risk in this cohort compared to the younger group. Since bleeding has been proven to be one of the most feared

complications of anticoagulant use among treating physicians, (205) this might have influenced physicians' prescribing decisions among elderly patients in our study despite their stroke risk.

We observed that elderly patients were at higher risk of major bleeding outcomes compared to younger ones. Older patients have organ function decline leading to increased risk of both bleeding and ischaemic events.(236) Moreover, the higher vulnerability of elderly patients may be related to drug-drug interactions due to polypharmacy further enhancing the risk of adverse effects associated with the use of antithrombotic agents.(239) Our elderly patient group was at higher risk of major bleeding as depicted by their mean HAS-BLED score, and higher rates of pre-existing renal impairment and previous bleeding disease history compared to the younger group. This might have predisposed them towards more major bleeding. When we grouped elderly patients based on whether or not they were prescribed an anticoagulant, those on anticoagulant therapy were at significantly higher risk of major bleeding compared to those not on anticoagulant therapy. The incidence rate of ICH was not higher among those on anticoagulant therapy. The mean HAS-BLED score between these two groups was also comparable but those on anticoagulant therapy had higher prevalence of CHF and embolic disease. Other age-related physiological changes and factors or suboptimal INR control may have been associated with this outcome and these need to be explored in similar studies in a larger population. We observed the incidence rate of major bleeding to be 2.9 per 100 person-years in the elderly patient group treated with anticoagulant therapy. Studies have reported major bleeding rates ranging from 1.1-13.1% per year with the use of anticoagulant therapy in elderly patients with AF.(236, 240-244) The rate of major bleeding among our elderly patient is thus comparable to the rates reported in other real-world studies.

Although older patients are known to have an increased risk of ischaemic events, (236) we did not observe significant difference in the incidences of TE overall and ischaemic stroke/SE outcomes in them compared to younger ones. Surprisingly, there was also a lack of difference in the incidence of stroke/SE between elderly patients treated and not treated with anticoagulants. The lack of difference in the rates between those treated and not treated could have been influenced by the small sample size of the study and consequently low number of events reported. Our rate of ischaemic stroke/SE was 2.1 per 100 person-years among elderly patient treated with anticoagulant therapy. Higher rates of ischaemic stroke/SE have been reported (7.1-8 per 100 person-years) in similar elderly populations in some real-world studies.(240, 245) One of these studies paradoxically reported that the incidence of stroke/SE was higher in extreme elderly patients receiving OAC than in those not receiving therapy.(245) Suboptimal INR control leading to higher incidence of stroke in anticoagulant-treated patients was one of the reasons proposed for such paradoxical finding in this study. In our study, this finding may be explained by the differences in baseline characteristics between groups, specifically the significantly higher proportions of elderly patients with a history of a TE event who were prescribed anticoagulants. Nonetheless, larger studies are needed to confirm the benefits and risks of anticoagulant therapy in reducing stroke/SE in elderly patients.

5.5 Conclusion

In this real-world longer-term follow-up study, underuse of anticoagulant therapy among elderly compared to younger patients with AF was evident. Elderly patients with AF were at higher risk of major bleeding but similar risk of TE compared to younger patients in this cohort. Elderly patients who were prescribed anticoagulants had a significantly higher risk of major bleeding

that those who were not, but interestingly, had a similar risk of TE events. This finding requires further investigation as it has important implications for management, and may have been due to the confounding effects of antiplatelet agents being used alone or in combination with anticoagulants, differences in the characteristics of elderly patients prescribed and not prescribed anticoagulants, poor control of anticoagulant therapy or other unknown underlying patient characteristics in elderly patients.

Chapter 6

Chapter 6: Concluding Discussion

6.1 Discussion

The Commonwealth Review of Anticoagulation Therapies in AF in Australia (2012) identified several issues to be addressed in regards to the proper management of patients with AF.(53) It also argued for the need for local data on which to base recommendations regarding the treatment of AF. As a starting point to addressing these recommendations, we initiated the TAF study, which is an observational study designed to comprehensively evaluate the management and outcomes of patients with AF. The studies included in this thesis explore the patient characteristics, antithrombotic prescribing patterns, factors associated with anticoagulant prescribing, rates of and risk factors of bleeding and TE-related hospitalisation for the patients enrolled in the TAF study between 1st January 2011 and 30th June 2012. These studies provide crucial local data to aid in the proper selection of antithrombotic drugs for individual patients to minimise the incidences of bleeding and TE in Australian patients. These findings will form the basis for ongoing research to monitor the management of AF in Tasmania in the future.

In chapter 2, the characteristics of patients with AF admitted to the three major Tasmanian hospitals and the appropriateness of antithrombotic prescribing according to guideline recommendations were presented. Firstly, this study showed that the patients in our study are comparable to the patient cohorts studied in recent AF-based registries, meaning that the Australian population is broadly comparable to other countries. Additionally, comparability of patient characteristics in terms of mean age and stroke risk with recent trials allows for the transferability of the benefits obtained from those trials to the Australian population. Secondly,

we also confirmed the suboptimal use of antithrombotic therapy in this cohort. All contemporary guidelines recommend prophylaxis with antithrombotic agents in people with AF and at least one other risk factor for stroke (7, 16) however discordance between AF guideline recommendations and anticoagulant prescribing patterns has been reported in various international studies.(103, 202) Our study also highlighted the underuse of anticoagulants according to guidelines. We observed underutilisation of anticoagulant therapy despite the high-risk of stroke in our population. This underutilisation could have been influenced by several factors such as HAS-BLED score exceeding the $CHADS_2$ score among those without any CIs, the majority of patients being elderly with multiple comorbidities in this cohort, belief that antiplatelet therapy alone is sufficient for stroke prophylaxis and lack of awareness of guideline recommendations.(194) Thirdly, we observed relatively high rate of prescribing of combination anticoagulant/antiplatelet therapy among patients newly initiated on therapy and in patients with existing AF at discharge. This issue warrants further investigation in order to identify the reasons for increase in combination prescribing as combination therapy is associated with a significantly higher risk of bleeding.(16) Overall, this study highlighted the need to identify the factors associated with anticoagulant prescribing among patients with AF and to compare the changes pattern of anticoagulant prescribing over the years in Tasmania.

In chapter 3, key factors associated with anticoagulant prescribing among patients with NVAF were presented. The results of a comparison between the anticoagulant utilisation patterns with earlier data in the same population were also reported. In this study we identified various factors that influence prescribers to prescribe anticoagulant therapy as thromboprophylaxis at discharge. Younger age, $CHADS_2$=1 (relative to 0), CHF and embolic disease history were

identified to be the significant predictors of anticoagulant prescribing in our population. CHF has been previously associated with a higher rate of oral anticoagulation use, (212) and previous TE is now clearly acknowledged as a risk factor for stroke through its inclusion in the CHA_2DS_2-VASc scoring system.(20) Benefits of anticoagulant therapy have been proven in clinical trials conducted among elderly patients (204, 216) and hence their use should not be overlooked among elderly high-risk groups. Our findings thus potentially suggest that the prescribers during this study period were less aware of the contemporary guideline recommendations of anticoagulant therapy among those with a $CHADS_2$ score $\geq$2.(7, 16) Fear of bleeding-related complications may have influenced their decision regarding the use of thromboprophylaxis in patient with $CHADS_2$ $\geq$2 and older age. Secondly, we observed improvements in anticoagulant prescribing among high-risk AF patients in Tasmania over the past 15 years and this most likely reflects increased focus on the importance of effective thromboprophylaxis as recommended in international guidelines, as well as the results of previous local intervention studies.(7, 16, 208) Future interventional studies comprising guideline dissemination strategies targeting the prescribers in multiple states of Australia can prove to be helpful to improve guideline adherence among the physicians. After evaluating the baseline details, we felt the need for examining the outcomes in terms of major bleeding and TE and the associated risk factors for such outcomes in this cohort.

In chapter 4, we have presented the rates of readmissions due to major bleeding or TE during short and longer-term follow-up periods among patients with newly diagnosed AF at the major hospital in Tasmania, Australia. We also identified the risk factors for readmission due to major bleeding or TE during longer-term follow-up. In this study, we observed a higher

incidence of major bleeding and TE during 3-month than longer-term follow up in other real world studies.(220, 221, 223). In comparing our rates to 'real-world' study data, the longer-term rate per 100 PY of stroke/SE events was comparable but the rate per 100 PY of major bleeding events was lower.(226) Our higher 3-month rates warrant the need for further investigation that involves the monitoring of anticoagulation control after initiation of warfarin. We also identified that history of MI was the only predictor for TE. A history of PVD and reduced eGFR were predictors of major bleeding-related readmissions. The risk of stroke and/or the composite TE endpoint (stroke, TIA, or SE) has been found to increase independently in the presence of vascular disease in patients with AF, (34) which is also reflected in the recent inclusion of MI as a risk factor for stroke in CHA_2DS_2-VASc. Our results suggest a need for a particular focus on the optimal prescribing in this group of patients so as to reduce the risk of stroke. Our findings suggest that these risk factors should be considered as potential 'red flags' when managing patients with AF, and patients with these conditions should receive special attention when managing concomitant AF. Since increasing age was identified as one of the negative predictors of anticoagulant prescribing in our population, we conducted a study to compare the patient characteristics, antithrombotic prescribing patterns, and rates of bleeding and TE outcomes between older and younger patients diagnosed with AF in our cohort.

In chapter 5, the results of examining and comparing the patient characteristics, antithrombotic prescribing patterns, and rates of bleeding or TE outcomes during longer-term follow-up between older and younger patients diagnosed with AF in Tasmania have been presented. In this study we observed underuse of anticoagulant therapy among high-risk elderly patients compared to the younger group despite its proven benefits.(204, 216) Bleeding risk has

been proven as one of the most feared complications of anticoagulant use among treating physicians. (205) This might have influenced physicians' prescribing decisions among elderly patients in our study despite their stroke risk. In this cohort, elderly patients had a higher mean HAS-BLED score, and higher rates of renal impairment and bleeding disease history. These factors might have predisposed this group to a higher rate of major bleeding outcomes compared to that in the younger patients. Our rate of bleeding with anticoagulant use among elderly patients was comparable to the rates (1.1-13.1% per year) reported in other real world studies.(236, 240-244) Our rate of ischaemic stroke/SE among the elderly patients treated with anticoagulant therapy was however lower (2.1 vs. 7.1-8 per 100 PY) than in some of the real-world studies.(240, 245) As mentioned above, further investigation that involves the monitoring of anticoagulation control after initiation of warfarin may explain our results more meaningfully.

In summary, our results suggest that though there has been some improvement in the use of anticoagulant therapy among high-risk patients with AF over the past 15 years in Tasmania, further developments are required so as to improve adherence to stroke risk stratification schemes for antithrombotic prophylaxis in AF and to potentially reduce stroke outcomes in our population. The observed issues of over-use of anticoagulant therapy in low risk patients, under-use in high risk patients and inappropriate use of combination therapy in patients with AF need to be addressed in order to minimise the unwanted risk of stroke and bleeding related complications in patients with AF.

6.2 Limitations

The results of our study are subject to some limitations of observational research such as the collection of non-randomized data and recording of incomplete and missing information. Recent hospitalisation for surgery may have constituted a reasonable indication for temporary cessation of anticoagulation, which may have influenced the findings regarding suboptimal anticoagulation. We only included patients with AF who experienced a hospitalisation meaning that they were potentially already at higher risk than 'average' Tasmanian patients with AF. This could limit the generalisability of our results to the broader Australian population. The rates of bleeding and TE in our study might have been influenced by the relatively small sample size of our study as well as due to the inclusion of patients with AF who experienced a hospitalisation. Lack of data regarding INR and TTR for those patients taking warfarin therapy led to difficulty in interpreting our findings related to our outcomes and predictors. Lastly, we had to assume the continuation of discharge antithrombotic therapy for patients not readmitted due to bleeding or TE. This could potentially limit the generalisability of our results in real-world practice, where changes in antithrombotic therapy could have been made during the entire follow-up period, even for those readmitted due to reasons other than bleeding or TE.

6.3 Future directions

While our study provides critical local data on the existing AF management pattern in an Australian sub-population prior to the PBS listing of DOACs, further investigations are required before implementing our findings to the clinical practice. The following recommendations are made as a result of this body of work:

1. Prospective studies enrolling prescribers in multiple states of Australia are required to substantiate our underutilisation findings and to better understand the existing barriers to guideline recommended antithrombotic prescribing. Interventional studies should then be designed to better support prescribers to assist in the identification and quantification of patient risk according to accepted international guidelines to optimise thromboprophylaxis and reduce the risk of thromboembolic and bleeding complications in this vulnerable patient group. We recommend that interventional studies should mainly address the issues of 1) under-use of anticoagulant therapy in high risk patients, 2) over-use of anticoagulant therapy in low risk patients, and 3) potentially inappropriate use of combination therapy in patients with AF. Such studies would be helpful in terms of exploring the reasons behind antithrombotic underutilisation. Such studies can even act as a good platform for disseminating information regarding recent AF management guidelines to the prescribers.

2. Interventional studies should be designed to optimise antithrombotic therapy prescribing in patients with history of PVD, MI and renal impairment so as to reduce bleeding and TE-related adverse events in patients with AF and these comorbidities.

3. Larger studies among extreme elderly (≥75 years) patients with AF, in multiple hospitals, are required so as to optimise stroke prophylaxis and to reduce bleeding associated adverse outcomes in this high-risk group.

4. We recommend the ongoing monitoring of prescribing practices in the light of increasing use of DOACs in Australia. Future analysis of TAF study data will help to explore the current trend of DOAC uptake after their PBS listing, and to identify their safety and efficacy profiles in the Australian population.

5. Lastly, we recommend the formulation of robust national AF management guidelines so as to better support prescribers to assist with guideline concordance. Formulation of national guidelines and their effective dissemination to physicians can improve the proportion of Australian patients receiving appropriate thromboprophylaxis for stroke prevention in AF.

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Chapter 7: References

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Appendices

Chapter 8: Appendices

8.1 Appendix A

Ethics approval from Human Ethics Committee of University of Tasmania

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HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

01 October 2012

Dr Leanne Chalmers
C/- Pharmacy

Sent via email

Dear Dr Chalmers

REF NO: H0012729
TITLE: Outcomes of antithrombotic therapy in a new era: the Tasmanian experience

Data collection sheet
Privacy Form
Tasmanian Health and Medical Low Risk

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on **28 September 2012**.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until approval is obtained in writing from the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested.
http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 28 September 2013. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Lauren Townsend
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8.2 Appendix B

Data collection sheet

FIRST ADMISSION

DEMOGRAPHICS AND MEDICAL HISTORY DETAILS

Patient ID: **Date of admission:**

Gender: ☐ **M** ☐ **F** **DOB:** **Date of discharge:**

Weight: **Admitted unit:** **Post Code:**

Final Diagnosis:

Lives: ☐ At home with family/carer ☐ At home alone ☐ Institutionalised

Smoking: ☐ Current smoker ☐ Ex- Smoker ☐ Never smoked ☐ Unsure

Alcohol: ☐ Yes ☐ No

***If yes*,** ☐ one or fewer alcoholic drinks per week ☐ 2-7 alcoholic drinks per week ☐ Unsure
☐ 8-14 alcoholic drinks per week ☐ 15 or more alcoholic drinks per week

Co-morbid conditions

MI ..... ☐ Yes..... ☐ No..... (history of medically documented MI)
CHF ..... ☐ Yes..... ☐ No..... (Documented history of CHF)
PVD..... ☐ Yes..... ☐ No..... (intermittent claudication, periph.arterial bypass for insufficiency, gangrene, actual arterial insufficiency, untreated)
CVD..... ☐ Yes..... ☐ No..... (HX of TIA, or CVA with no or minor sequelae)
Dementia ..... ☐ Yes..... ☐ No..... (Chronic progressive syndrome due to disease of brain in which there is disturbance of multiple higher cortical function including memory, thinking ,orientation, comprehension, calculation, learning capability, language, and judgement)
Chronic Respiratory Disease ..... ☐ Yes..... ☐ No..... (symptomatic dyspnea due to chronic respiratory conditions (asthma, COPD, bronchitis)
Ulcer Disease..... ☐ Yes..... ☐ No..... (PUD)
Connective tissue disease ..... ☐ Yes..... ☐ No..... (SLE,RA,Scleroderma, sjogren's disease)
AIDS ..... ☐ Yes..... ☐ No..... (most advanced stages of HIV infection defined by the occurrence of any of more than 20 opportunistic infections or HIV-related cancers)
Diabetes..... ☐ Yes..... ☐ No..... (diabetes with medication)
Diabetes with end organ damage ..... ☐ Yes..... ☐ No..... (retinopathy,neuropathy,nephropathy)
Moderate or severe renal disease..... ☐ Yes..... ☐ No..... (Cr>265 micromol/l, dialysis, transplantation, uraemic syndrome) (At discharge)
Hemiplegia (or paraplegia) ..... ☐ Yes..... ☐ No..... (Hemiplegia or paraplegia)
Any solid tumor ..... ☐ Yes..... ☐ No..... (any malignancy incl. lymphoma/leukaemia for updated criteria)

Leukaemia..... ☐ Yes..... ☐ No..... (CML, CLL, AML,ALL,*PV)
Lymphoma ..... ☐ Yes..... ☐ No..... (NHL,Hodgkin's, Waldenstrom, multiple myeloma)
Moderate or severe liver disease..... ☐ Yes..... ☐ No..... (cirrhosis with portal +/- variceal bleeding) (At discharge)
Mild liver disease..... ☐ Yes..... ☐ No..... (cirrhosis without portal HT, chronic hepatitis)
Metastatic solid tumor ..... ☐ Yes..... ☐ No
Valvular heart disease ..... ☐ Yes..... ☐ No.....
Other Embolic events ..... ☐ Yes..... ☐ No..... (pulmonary embolism, DVT)
Hypertension..... ☐ Yes..... ☐ No..... *Systolic BP (Discharge):*
Diastolic BP:

Uncontrolled hypertension (SBP>160mmHg) (Discharge)..... ☐ Yes ☐ No
IHD (angina), other vascular disease (aortic plaque) ☐ Yes ☐ No

Medications on Admission

	DRUG	DOSE	FREQUENCY
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			

Notes:

Allergies to antithrombotics? ☐ No ☐ Yes - Details:

Duration of AF in a patient: ☐ First detected ☐ Other:

Rhythm recorded: ☐ Paroxysmal AF ☐ Persistent AF ☐ Permanent AF

INR on admission (only if taking warfarin):

Risk factors for bleed (HAS BLED)

☐ Labile INR (<60% time in therapeutic range/ unstable/high INRs)

☐ Prior major bleeding or predisposition to bleeding (Haemophilia etc.)

CI to antithrombotic therapy: ☐ Yes ☐ No

☐ Psychosis ☐ H/O asthma induced by NSAIDs ☐ Pregnancy

IN-PATIENT ADMISSION DETAILS

Reason for admission

☐ Related to AF ☐ Thromboembolic event (Ischaemic stroke, TIA, PE or other)

☐ Bleeding (ICH or other) ☐ Unrelated to AF-related cardiovascular admission ☐ None of the above

If due to bleeding

☐ Bleeding secondary to INR> 10

☐ Bleeding due to DDIs (e.g. warfarin with metronidazole, cephalexin, tamoxifen

☐ GI bleeding due to excess alcohol intake (e.g. 48 stubbies in 2 days in patient taking aspirin)

☐ Fatal ☐ Major ☐ Minor See Definition

Brain imaging (for confirmation) ☐ Head CT ☐ MRI

Anatomic site of haemorrhage

☐ Intracranial ☐ Upper gastrointestinal ☐ Lower gastrointestinal ☐ Intraspinal ☐ Pericardial

☐ Retroperitoneal ☐ Other

Bleeding due to antithrombotic was managed with:

☐ Drug stopped ☐ Fluid replacement ☐ Vitamin K1 ☐ Fresh frozen plasma

☐ Tranexamic acid ☐ Prothrombinex-VF ☐ Oral charcoall ☐ Factor VIIa

☐ Hemodialysis ☐ Charcoal Haemofiltration ☐ Inotropic agents

Transfusion (units or millilitres)

☐ Whole blood ☐ packed red blood cells ☐ platelets ☐ other blood products

If due to thromboembolism: Thromboembolism was managed with

☐ Anticoagulant therapy (LMWH, warfarin)

☐ Thrombolytic therapy (streptokinase, tissue plasminogen activator, urokinase)

Details of Medication administered to manage bleeding or stroke

Drug	Doses	Duration

Notes:

Details of Procedures used to manage bleeding or stroke

Procedures	Rationale

Notes:

Antithrombotic therapy (during hospital stay)

	DRUGS	DOSE	FREQUENCY
1			
2			
3			
4			
5			

INR values throughout admission

Day	INR	Warfarin (Doses in mg)	Notes	Day	INR	Warfarin (Doses in mg)	Notes

Inpatient care

☐ Investigations

☐ Cardioversion (electrical or pharmacologic cardioversion)

☐ Surgery (surgical procedures)

Adverse drug reaction observed (if any, defined)

Details:

Severity	☐ Mild	☐ Moderate	☐ Severe	☐ Fatal
Causality	☐ Doubtful	☐ Possible	☐ Probable	☐ Definite
Preventable	☐ Yes	☐ NO		

DISCHARGE DETAILS

Laboratory reports on discharge:

Test	Values	Notes
Serum creatinine (60-115 µmol/L)		
GFR (>90 Ml/min/1.73m^2)		
Serum albumin (32-45 g/L)		
ALP (25-100 U/L)		
ALT (<35 U/L)		
GGT (F<30, M<50 U/L)		
Total bilirubin: (<20 µmol/L)		
Hb (130-175 g/L)		
Platelet count (160-420/nL)		
PTT (10-14 seconds)		
APTT (25-45 seconds)		
TT (14-16 seconds)		
Systolic BP (120 mmHg)		
Diastolic BP (80 mmHg)		

Patient outcome

☐ Complete/near-complete recovery (able to return to pre-admission level of function)

☐ Mild to moderate deficit (deficits present, but patient can perform activities of daily living, such as dressing and feeding, with or without assistance)

☐ Severe deficit (required assistance to complete activities of daily living)

☐ Death

Reasons for not initiating or discontinuation antithrombotic:

☐ Poor adherence ☐ Falls ☐ Ineffective

☐ Patient refusal ☐ Physicians decision ☐ ADRs

***Antithrombotic therapy*:**

☐ Newly initiated ☐ Changed

☐ Continued ☐ Stopped

☐ Recommendation for commencement in community ☐ No therapy ☐ N/A

Details:

Discharge medications:

	DRUG	DOSE	FREQUENCY
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Notes:

RE-ADMISSION

DEMOGRAPHICS AND MEDICAL HISTORY DETAILS

Patient ID: **Date of admission:**

Gender: ☐ **M** ☐ **F** **DOB:** **Date of discharge:**

Weight: **Admitted unit:** **Post Code:**

Final Diagnosis:

Lives: ☐ At home with family/carer ☐ At home alone ☐ Institutionalised

Smoking: ☐ Current smoker ☐ Ex- Smoker ☐ Never smoked ☐ Unsure

Alcohol: ☐ Yes ☐ No

***If yes*,** ☐ one or fewer alcoholic drinks per week ☐ 2-7 alcoholic drinks per week ☐ Unsure
☐ 8-14 alcoholic drinks per week ☐ 15 or more alcoholic drinks per week

Co-morbid conditions

MI ..... ☐ Yes..... ☐ No..... (history of medically documented MI)
CHF ..... ☐ Yes..... ☐ No..... (Documented history of CHF)
PVD..... ☐ Yes..... ☐ No..... (intermittent claudication, periph.arterial bypass for insufficiency, gangrene, actual arterial insufficiency, untreated)
CVD..... ☐ Yes..... ☐ No..... (HX of TIA, or CVA with no or minor sequelae)
Dementia ..... ☐ Yes..... ☐ No..... (Chronic progressive syndrome due to disease of brain in which there is disturbance of multiple higher cortical function including memory, thinking ,orientation, comprehension, calculation, learning capability, language, and judgement)
Chronic Respiratory Disease ..... ☐ Yes..... ☐ No..... (symptomatic dyspnea due to chronic respiratory conditions (asthma, COPD, bronchitis)
Ulcer Disease..... ☐ Yes..... ☐ No..... (PUD)
Connective tissue disease..... ☐ Yes..... ☐ No..... (SLE,RA,Scleroderma, sjogren's disease)
AIDS..... ☐ Yes..... ☐ No..... (most advanced stages of HIV infection defined by the occurrence of any of more than 20 opportunistic infections or HIV-related cancers)
Diabetes..... ☐ Yes..... ☐ No..... (diabetes with medication)
Diabetes with end organ damage ..... ☐ Yes..... ☐ No..... (retinopathy,neuropathy,nephropathy)
Moderate or severe renal disease..... ☐ Yes..... ☐ No..... (Cr>265 micromol/l, dialysis, transplantation, uraemic syndrome) (At discharge)
Hemiplegia (or paraplegia) ..... ☐ Yes..... ☐ No..... (Hemiplegia or paraplegia)
Any tumor ..... ☐ Yes..... ☐ No..... (any malignancy incl. lymphoma/leukaemia for updated criteria)
Leukaemia..... ☐ Yes..... ☐ No..... (CML, CLL, AML,ALL,*PV)
Lymphoma..... ☐ Yes..... ☐ No..... (NHL,Hodgkin's, Waldenstrom, multiple myeloma)
Moderate or severe liver disease..... ☐ Yes..... ☐ No..... (cirrhosis with portal +/- variceal bleeding) (At discharge)
Mild liver disease..... ☐ Yes..... ☐ No..... (cirrhosis without portal HT, chronic hepatitis)

Metastatic solid tumor .....☐ Yes..... ☐ No
Valvular heart disease .....☐ Yes..... ☐ No.....
Other Embolic events .....☐ Yes..... ☐ No..... (pulmonary embolism, DVT)
Hypertension.....☐ Yes..... ☐ No..... *Systolic BP (Discharge):*
Diastolic BP:

Uncontrolled hypertension (SBP>160mmHg) (Discharge)..... ☐ Yes ☐ No
IHD (angina), other vascular disease (aortic plaque) ☐ Yes ☐ No

Previous medication history

	DRUG	DOSE	Frequency
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Notes:

Allergies to antithrombotics? ☐ No ☐ Yes - Details:

Duration of AF in a patient: ☐ First detected ☐ Other:
Rhythm recorded: ☐ Paroxysmal AF ☐ Persistent AF ☐ Permanent AF

INR on admission (only if taking warfarin):

Risk factors for bleed (HAS BLED)

☐ Labile INR (<60% time in therapeutic range/ unstable/high INRs)
☐ Prior major bleeding or predisposition to bleeding (Haemophilia etc.)

CI to antithrombotic therapy: ☐ Yes ☐ No
☐ Psychosis ☐ H/O asthma induced by NSAIDs ☐ Pregnancy
☐ Prior major bleeding or predisposition to bleeding (Haemophilia etc.)

IN-PATIENT ADMISSION DETAILS

Reason for re-admission

☐ Related to AF ☐ Thromboembolic event (Ischaemic stroke, TIA, PE or other)
☐ Bleeding (ICH or other) ☐ Unrelated to AF (e.g. MI)

If due to bleeding

☐ Bleeding secondary to INR> 10
☐ Bleeding due to DDIs (e.g. warfarin with metronidazole, cephalexin, tamoxifen
☐ GI bleeding due to excess alcohol intake (e.g. 48 stubbies in 2 days in patient taking aspirin)
☐ Fatal ☐ Major ☐ Minor See Definition

Brain imaging (for confirmation) ☐ Head CT ☐ MRI

Anatomic site of haemorrhage

☐ Intracranial ☐ Upper gastrointestinal ☐ Lower gastrointestinal ☐ Intraspinal ☐ Pericardial
☐ Retroperitoneal ☐ Other

Bleeding due to antithrombotic was managed with:

☐ Drug stopped ☐ Fluid replacement ☐ Vitamin K1 ☐ Fresh frozen plasma
☐ Tranexamic acid ☐ Prothrombinex-VF ☐ Oral charcoall ☐ Factor VIIa
☐ Hemodialysis ☐ Charcoal Haemofiltration ☐ Inotropic agents

Transfusion (units or millilitres)

☐ Whole blood ☐ packed red blood cells ☐ platelets ☐ other blood products

If due to thromboembolism: Thromboembolism was managed with

☐ Anticoagulant therapy (LMWH, warfarin)
☐ Thrombolytic therapy (streptokinase, tissue plasminogen activator, urokinase)

Details of Medication administered to manage bleeding or stroke

Drug	Doses	Duration

Notes:

Details of Procedures used to manage bleeding or stroke

Procedures	Rationale

Notes:

Antithrombotic therapy (during hospital stay)

	DRUGS	DOSE	FREQUENCY
1			
2			
3			
4			
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INR values throughout admission

Day	INR	Warfarin (Doses in mg)	Notes	Day	INR	Warfarin (Doses in mg)	Notes

Inpatient care

☐ Investigations

☐ Cardio version (electrical or pharmacologic cardioversion)

☐ Surgery (surgical procedures)

Adverse drug reaction observed (if any, defined)

Details:

Severity	☐ Mild	☐ Moderate	☐ Severe	☐ Fatal
Causality	☐ Doubtful	☐ Possible	☐ Probable	☐ Definite
Preventable	☐ Yes	☐ NO		

DISCHARGE DETAILS

Laboratory reports on discharge:

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Notes: